INTRODUCTION TO VOLUME 4: ADDITIONS TO AND SUBSTITUTIONS AT C–C π-BONDS

The first edition of Comprehensive Organic Synthesis (Eds. B. M. Trost and Ian Fleming) has had a very successful impact in the international organic chemistry committee; thus, we have been very happy to be part of the second edition in charge of volume 4, entitled 'Additions to and Substitutions at C–C π-Bonds.' The vastness of the development in this field has gained such dimensions that it is very difficult to obtain a facile access to the topics of interest for nonspecialists. In this volume, which contains 23 chapters with a nice selective coverage of the literature, the reader will find all aspects of the additions to and substitution at C–C π-bonds.

In the first Chapter (4.01), the nucleophilic addition of various types of stabilized nucleophiles to electron-deficient alkenes, alkynes, and allenes leading to racemic products is discussed in detail. Electrophile trapping of the carbanion intermediate generated from nucleophilic addition is the next topic (Chapter 4.02), in which asymmetric tandem reactions are also included. The enantioselective conjugate addition (ECA) of nucleophiles to electron-deficient alkenes represents one of the most powerful methods to furnish optically active compounds, which has been widely used in organic synthesis. In the past two decades, significant breakthroughs have been observed in this field, including the design of new types of catalysts and extending the substrate scope. Based on the catalytic mode, this topic has been divided into two chapters (Chapter 4.03: Organocatalysis and Chapter 4.04: Transition Metal Catalysis). Addition of H–X (Chapter 4.05) and X–Y (Chapter 4.06) reagents to C–C π-bonds are among the most straightforward methods to construct heteroatom-containing compounds. In Chapter 4.05, to avoid overlapping with other related chapters, the metal-mediated addition of H–X to C–C multiple bonds has not been covered, except for a few examples of mercury- and gold-mediated reactions. In Chapter 4.06, three different reaction pathways including ionic, radical, and transition metal catalyzed process are demonstrated. In Chapter 4.07, electrophilic cyclization reactions leading to heterocyclic compounds in many different ring sizes via *endo*- or *exo*-cyclization modes, depending on the types of electrophiles and substrates, have been discussed in detail. The generation, reactivity, and reaction pattern of the aryl radical and arynes are separately summarized in Chapters 4.08 and 4.09. In Chapter 4.10, stoichiometric nucleophilic addition reactions of alkynes, alkenes, and allenes coordinated to mononuclear transition metal centers are summarized, which represent the fundamental steps in a rapidly growing number of catalytic processes mediated by transition metal complexes. The general methods to generate the various allyl metal complexes and their corresponding reactions with nucleophiles are summarized in Chapter 4.11. The focus of this field has shifted to metal-catalyzed enantioselective allylic substitution with nucleophiles since the 1990s. The recent progress of radical addition to C–C π-bonds is discussed in Chapters 4.12 (intermolecular cases) and 4.13 (intramolecular cases) separately. The generation and reactivity of radicals, and the steterocontrol of the reactions, as well as synthetic applications, are the major topics for these two chapters. The palladium-catalyzed vinyl substitution (Chapter 4.14), often called Heck reaction, has been extensively studied and well summarized in all the aspects of the reaction including the proper choice of reactants, solvents, bases, additives, catalyst precursors, and ligands necessary for optimal reaction conditions and application in total synthesis of complex molecules. Organometallic compounds are important and very useful reagents in organic synthesis. The carbometallation, heterometallation, and bismetallation of C–C π-bonds are believed to offer facile access to mono- and bismetallic compounds. Much progress has been made in the field of carbometallation and heterometallation reactions of alkenes, alkynes, and allenes since 1991, which has been nicely summarized in Chapter 4.15. Besides the bismetallation, the recent advance of the related bismetallative reaction has also been discussed in Chapter 4.16. Carbonyl group-containing compounds are very useful in organic synthesis and industry due to their rich transformations. The hydroacylation, hydroformylation, and related carbonyl reactions of C–C π-bonds are the most atom-economic ways to bring the carbonyl group to these C–C π-bonds; their intrinsic atom-economic nature and the use of cheap feedstocks render this process particularly attractive for the production of commodities. Chapters 4.17 and 4.18 demonstrate the recent progress of this field in the past two decades from the aspects of catalysts, substrate scope, and selectivity. The cyclopropane and cyclopropene units have attracted growing interest over the years due to their unique high strain bonding properties, numerous applications in diverse chemical transformations, and importance in natural product synthesis and drug development. Two chapters cover this topic: one is the methylene and nonfunctionalized alkylidene transfer to form cyclopropanes (Chapter 4.19) and the other is addition of ketocarbenes to alkenes, alkynes, and aromatic systems (Chapter 4.20). Since Huisgen's breakthrough on 1,3-dipolar cycloaddition reactions, the dipolar cycloaddition reactions have received widespread attention in the synthetic community. Chapters 4.21 (intramolecular reactions) and 4.22 (intermolecular reactions) summarize the recent advances in this area including the highlights of the various dipoles, the selectivity control and synthetic applications in organic synthesis. Finally, the last Chapter (4.23) focuses on the progress of the Stetter reaction, which stands as a powerful approach to 1,4-dicarbonyl motif from aldehyde and Michael acceptor through the catalysis of a variety of carbenes. This chapter provides a review of intra- and intermolecular Stetter reactions with an emphasis on recent enantioselective variants and on their application to total synthesis.

The authors spent a lot of time and effort in collecting and classifying the literature, writing and revising the manuscripts, and checking the galley proofs of the final typeset chapters. It is an exciting experience for us to work with these specialists in this field.

Their great contributions to this volume are highly appreciated. We are also grateful to the Editors-in-Chief Paul Knochel and Gary Molander and to the publisher for their kind help.

Shengming Ma
Shanghai Institute of Organic Chemistry and East China Normal University, China

Junliang Zhang
East China Normal University, Shanghai, China

4.01 Stabilized Nucleophiles with Electron Deficient Alkenes, Alkynes, Allenes

W-Q Chen, Chinese Academy of Sciences, Lanzhou, China
J-A Ma, Tianjin University, Tianjin, China

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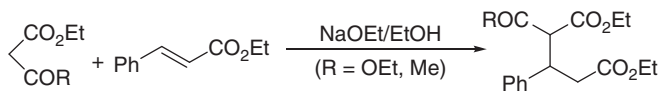
4.01.1 Introduction

Since Michael reported the addition of the sodium salt of both diethyl malonate and ethyl acetoacetate to ethyl cinnamate in 1887 (referred to as Michael reaction, equation 1 in Scheme 1),[1] this conjugate reaction has been considerably extended by the employment of various nucleophilic carbon and heteroatom donors, electron-deficient acceptors, catalysts, and various media. Today, this conjugate addition represents one of the most fundamental and useful constructive methods for the formation of carbon–carbon and carbon–heteroatom bonds in organic chemistry. Furthermore, the broad potential of this transformation has been embodied in the synthesis of numerous natural products and biologically active compounds.



(1)

Scheme 1

Although the related topics have been mentioned in many reviews over recent decades,[2] the aim of this chapter is to provide an up-to-date overview of recent advances and applications in the conjugate additions of stabilized nucleophiles (Nu) to electron-deficient alkenes, alkynes, and allenes with various electron-withdrawing groups (EWG) (Figure 1). In particular, emphasis

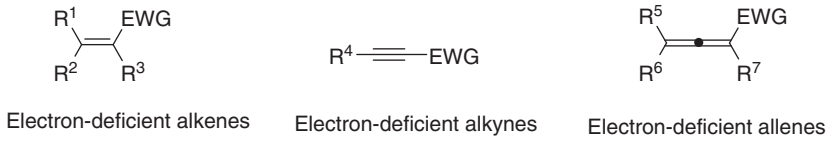


Figure 1 The structures of electron-deficient alkenes, alkynes, and allenes.

will be placed on those methods with potential for organic synthesis. Accordingly, some early references will be summarized briefly to have all the key information in hand. It should be pointed out that only additions of stabilized nucleophilic donors for the formation of Nu–C bonds are included here. The additions of reactive nucleophiles (organolithiums, organozincs, Grignards, cuprates, etc.) and carbon ligands, as well as asymmetric nucleophilic additions, will be covered in related chapters of this volume.

4.01.2 Electron-Deficient Alkenic π-Systems

4.01.2.1 Carbon Nucleophiles

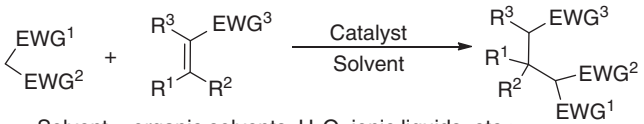
This section mainly focuses on the carbon–carbon bond-forming reactions via the conjugate additions of stabilized carbon nucleophiles (such as 1,3-dicarbonyl compounds, α-nitro carbonyl compounds, α-nitrile carbonyl compounds, malonitrile, cyanide, aldehyde or ketone enolates, and enamines) to electron-deficient alkenic acceptors (such as α,β-unsaturated aldehydes, ketones, esters, amides, nitriles, nitroolefins, and vinyl sulfones). These conjugate addition reactions typically occur in organic solvent under basic conditions, but ionic liquid, water, and polyethylene glycol have also been used. Many Lewis acids, and metal complexes (such as aluminum, copper, nickel, magnesium, scandium, palladium, and iridium complexes),[3] bases, and organocatalysts (including various amines, (thio)ureas, and Brønsted acids) have been shown to catalyze/promote the conjugate additions. In this context, these additions are divided into intermolecular and intramolecular processes, respectively.

4.01.2.1.1 Intermolecular additions

The intermolecular conjugate addition of carbon nucleophiles to electron-deficient alkenes offers a convenient and convergent approach to prepare various multifunctional substituted compounds, which can be converted into cyclic-, dicyclic-, or fused cyclic compounds.

4.01.2.1.1.1 Active methylene carbon nucleophiles

Conjugate additions using active methylene carbon nucleophiles have been receiving considerable attention since both EWG provide an outstanding enhancement of the hydrogen acidity at the α-position (equation 2 in Scheme 2). In addition to the procedures that work in homogeneous conditions, many heterogeneous systems have also been employed in the conjugate additions of active methylene carbon nucleophiles.[4] Some activating techniques such as microwave or ultrasound irradiation could also improve the efficiency of known catalysts, especially those working in heterogeneous and solvent-free conditions.[5] In addition, many new reagents/substrates have been employed in the conjugate additions of active methylene carbon nucleophiles to electron-deficient alkenes. More significantly, the insertion of multifunctional groups within the adducts may provide further opportunity for synthetic transformations, and allows access to various target molecules of practical interest.

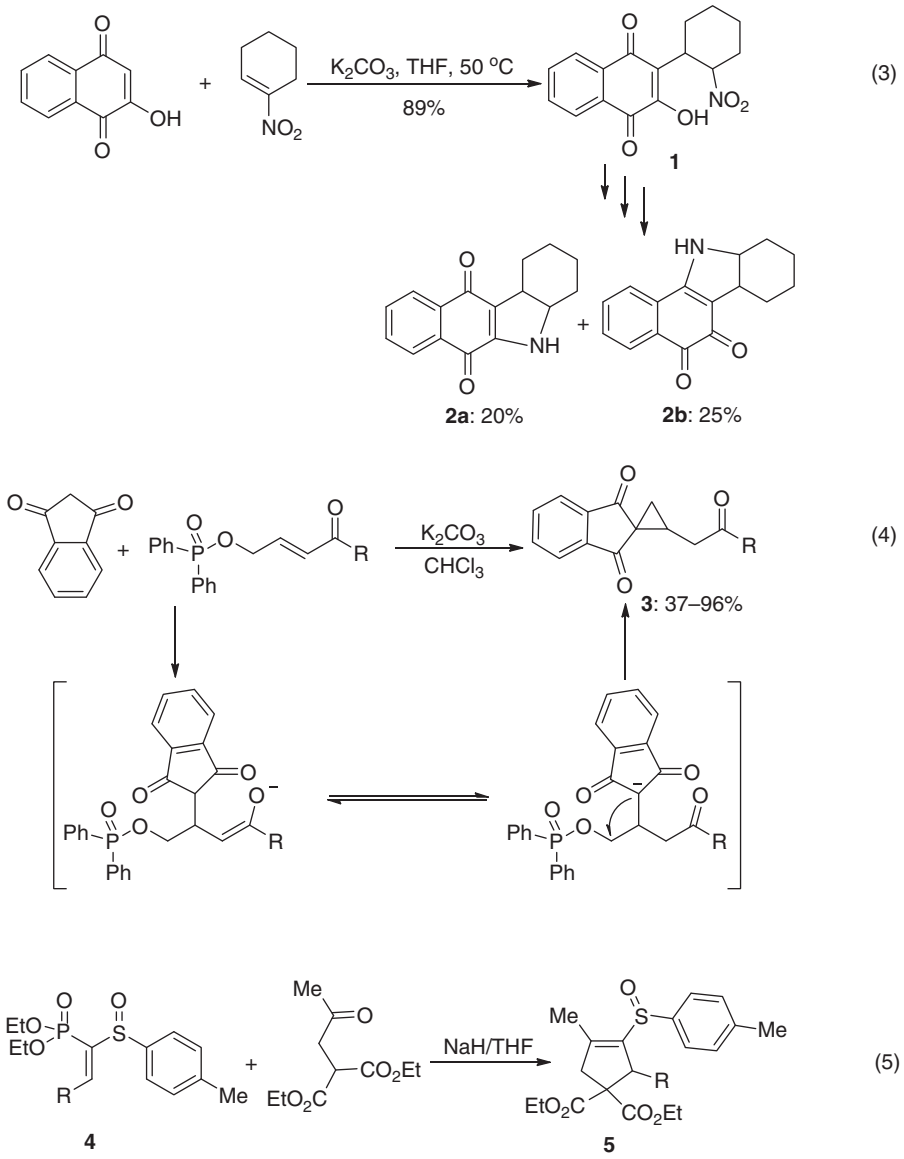


(2)

Solvent = organic solvents, H_2O, ionic liquids, etc.;
Catalyst = Inorganic and organic bases, Lewis acids, etc.;
EWG = COR, CN, SO_2Ph, NO_2, etc.

Scheme 2

Traditionally, the conjugate addition reactions of 1,3-dicarbonyl compounds are catalyzed by strong bases such as alkali metal alkoxides or hydroxides. Many efforts have been focused on the conjugate addition-triggered tandem transformations.[6] For example, under the catalysis of K_2CO_3, the conjugate addition of quinone to nitro cycloalkene delivered the adduct **1**,[6c,f] which could be further converted into benzocarbazoledione derivatives **2** via reduction and cyclization (equation 3 in Scheme 3). Using K_2CO_3 as base, Russo and coworkers developed a Michael-initiated ring-closure transformation for the construction of the cyclopropane unit. The reaction of 1,3-indandione with γ-hydroxyenone-derived diphenyl phosphinates at room temperature proceeded via intermolecular conjugate addition, proton transfer, and intramolecular cyclopropanation to give the expected cyclopropanes **3** with homologated carbonyl moiety (equation 4 in Scheme 3).[6e] Mikołajczyk and coworkers demonstrated that

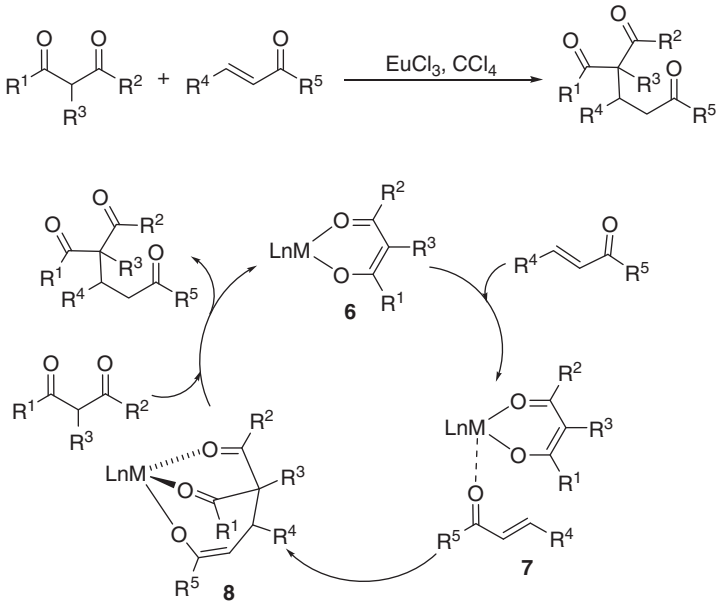


Scheme 3

the addition reaction of sodium salt of diethyl 2-(2-oxopropyl)malonate to α-phosphorylvinyl sulfoxides **4** underwent to give cyclopentene sulfoxides **5** in a tetrahydrofuran (THF) solution (equation 5 in Scheme 3).[6b] This transformation was based on the tandem conjugate addition/Horner olefination sequence. Using optically active α-phosphorylvinyl sulfoxides, this approach delivered a series of enantiomeric cyclic vinyl sulfoxides.

However, there are a number of disadvantages associated with strong base catalysis, including side reactions of ester solvolyses, aldol processes, or retro-Claisen-type decompositions. The application of Lewis acids and metal complexes as catalysts is a mild and efficient alternative to base catalysis for such addition reactions. In 1993, Scettri and coworkers reported $EuCl_3$ in anhydrous CCl_4 to be an efficient catalyst for the conjugate addition reaction (equation 6 in Scheme 4).[7a] It was the first lanthanide salt to be applied in this field, and it also broke the previous unwritten rule that either the catalyst had to be a complex bearing dionato ligands, or the anion had to be a Brønsted base such as acetate, so that dionato species would be readily generated *in situ* from the 1,3-dicarbonyl compounds. There have been some improvements on Scettri's procedure since the original research. Feringa and Keller described the conjugate additions in aqueous media at room temperature by employing $Yb(OTf)_3$,[7b] whereas three other research groups introduced $FeCl_3$ as the catalyst.[7c–f] β-Diketones or β-ketoesters with methyl vinyl ketone (MVK) were cleanly converted into the corresponding Michael reaction products within a few hours at room temperature, with quantitative yields being achieved in most cases.

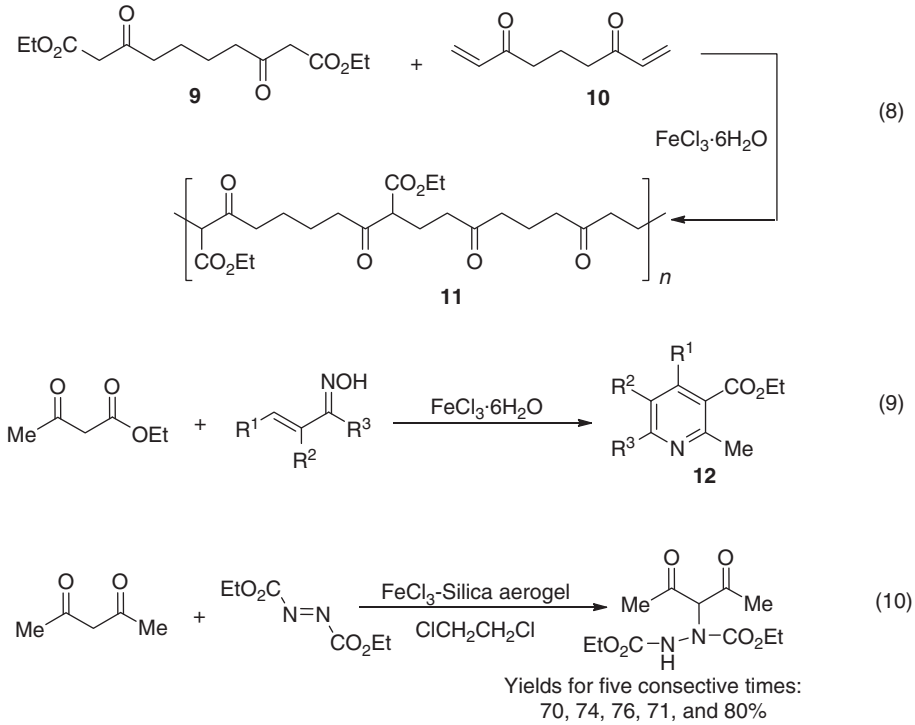
The mechanism was proposed as shown in equation 7 of Scheme 4.[7g] Under the reaction conditions, 1,3-dicarbonyl compound is coordinated to the metal center into 1,3-diketonato species **6**, in which the ligand is planar and is particularly stabilized



Scheme 4

by π-delocalization, and α,β-unsaturated carbonyl compound is proposed to coordinate at a vacant coordination site to form the complex **7**. Subsequently, the central carbon atom of the dionato ligand is thought to be alkylated by the coordinated α,β-unsaturated carbonyl reactant to give the intermediate **8**. Finally, the adduct is liberated readily and the complex **6** can be regenerated through substrate exchange.

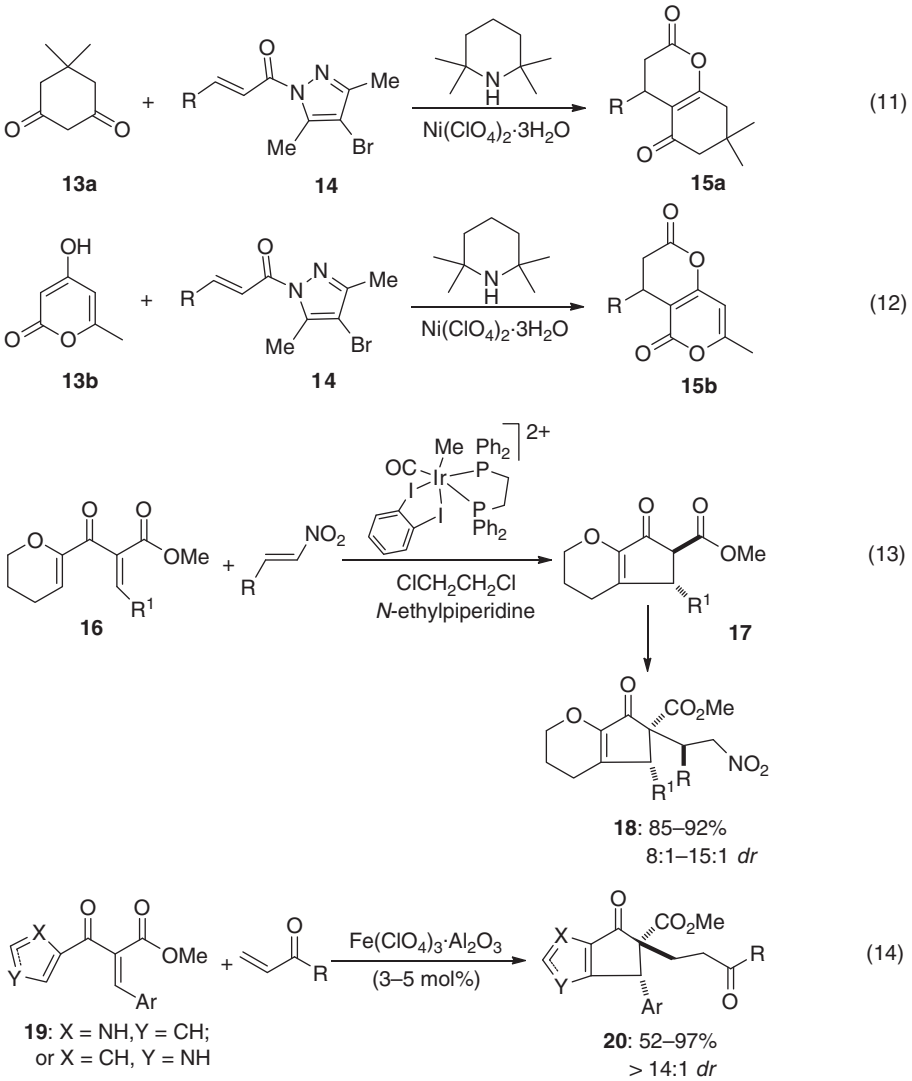
Based on the use of hydrated iron(III) chloride ($FeCl_3{\cdot}6H_2O$), the formation of polymers **11** was realized by reaction of the bis-β-ketoester **9** with the bis-vinyl-ketone **10** (equation 8 in Scheme 5).[8a] A further development has been reported by Tkachev's group. The conjugate addition of ketoesters to oximes of unsaturated ketones affords pyridines **12** (equation 9 in Scheme 5).[8b] Furthermore, iron(III) species have been used in solid supports. Thus, Fe(III)-exchanged fluorotetrasilicic mica catalyzes reactions of β-ketoesters with MVK.[8c] However, the catalyst is limited to this electrophile, but is recovered and reused. Notably, silica



Scheme 5

aerogel–ferrihydrite nanocomposite can be used as a recoverable catalyst in the conjugate addition of acetylacetone to dialkyl azodicarboxylates. The catalytic solid can be reused without loss of activity (equation 10 in Scheme 5).[8d]

Other metal complexes, such as palladium, scandium, copper, aluminum, nickel, magnesium, indium, and ruthenium, can also catalyze the addition of active methylene compounds to Michael acceptors.[9] A double catalytic activation conjugate addition reaction of cyclic 1,3-dicarbonyl compounds **13a** and **13b** with 1-(2-alkenoyl)-4-bromo-3,5-dimethylpyrazoles **14** was reported by Kanemasa and coworkers (equations 11 and 12 in Scheme 6).[10a–d] This reaction can be promoted by the use of nickel(II) perchlorate hexahydrate as Lewis acid catalyst, while bulky 2,2,6,6-tetramethylpiperidine (TMP) can be successfully employed as base catalyst. The pyrazole moiety acts as a pseudohalogen leaving group after the initial conjugate addition. The corresponding enol lactones **15a** and **15b** were obtained in 41–97% yields.

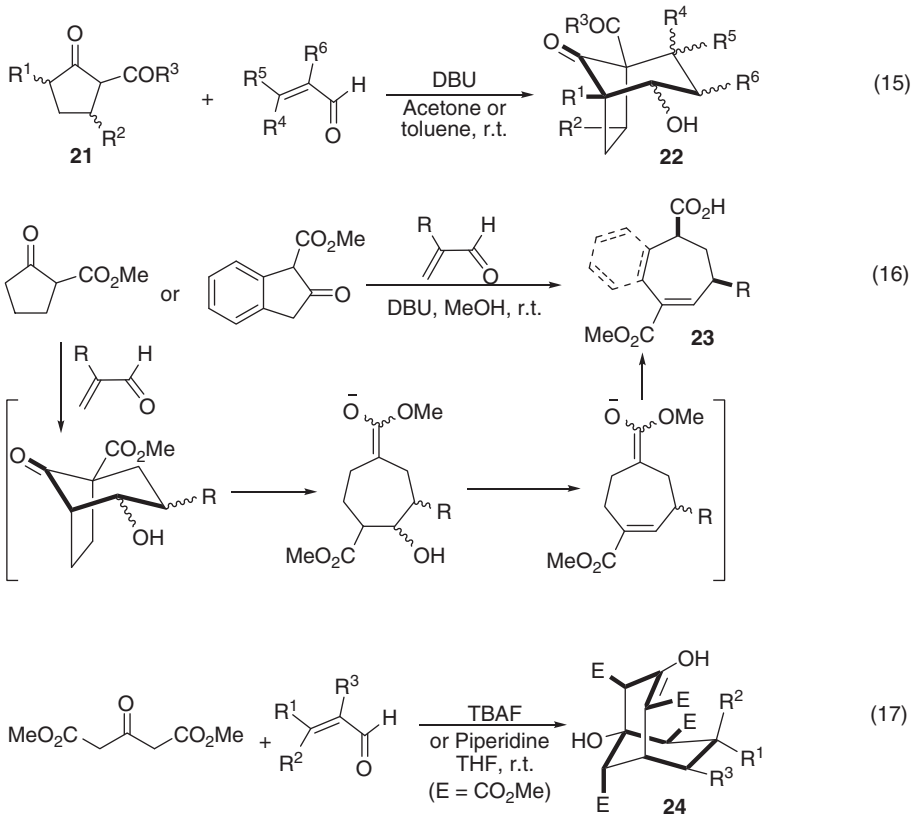


Scheme 6

Another application of the double catalytic activation conditions, described by Frontier and coworkers, was the reaction of alkylidene β-ketoesters **16** with nitroalkenes through a tandem Nazarov cyclization-conjugate addition process (equation 13 in Scheme 6).[10e] Both base and indium complex are necessary for this tandem reaction. The tandem products **18** were generated in high diastereoselectivity, with only two of four possible diastereomers observed. If no base was added, only Nazarov product **17** was formed. In the absence of indium complex, the reaction between **17**, nitrostyrene, and *N*-ethylpiperidine was very slow.

A similar tandem Nazarov/conjugate sequence of pyrrole-substituted alkylidene β-ketoesters **19** with enones has also been accomplished (equation 14 in Scheme 6).[10f] In the presence of alumina-supported iron(III) perchlorate [$Fe(ClO_4)_3{\cdot}Al_2O_3$], 4,5-dihydrocyclopenta[*b*]pyrrol-6(1*H*)-one or 5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one derivatives **20** were produced with excellent diastereoselectivity. Furthermore, this one-pot sequential transformation could proceed in an ionic liquid [bmim][NTf_2], and the products were obtained in good yields after five repetitions of the reaction without any addition of the catalyst.[10g]

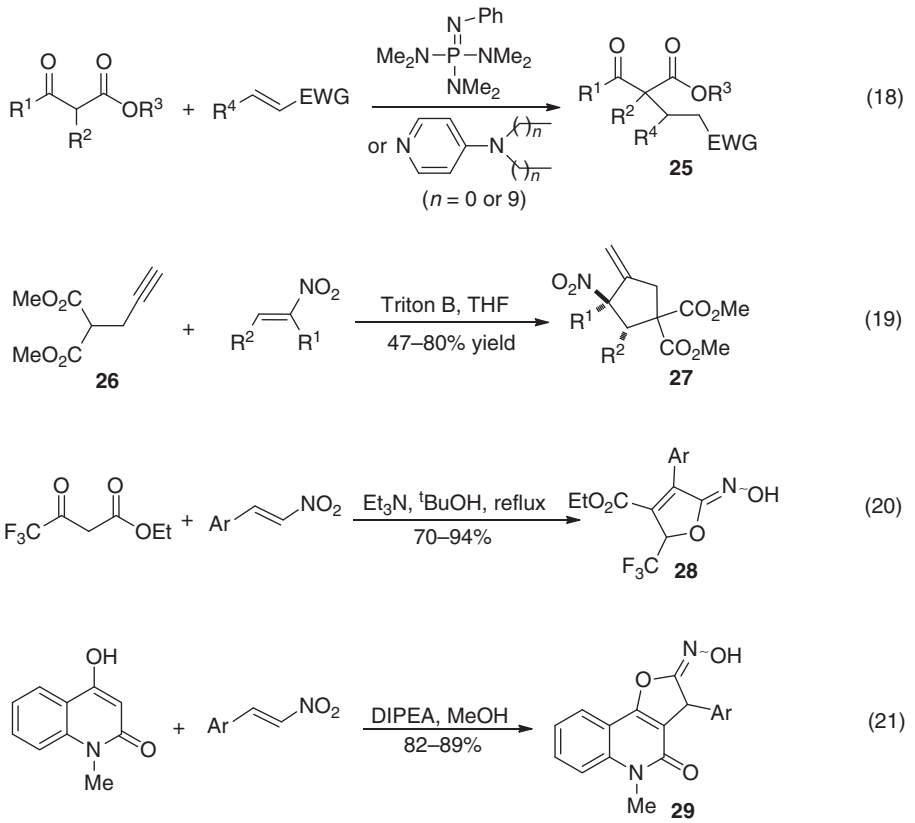
For the conjugate addition reactions of 1,3-dicarbonyl compounds, organic bases have emerged as powerful alternatives to commonly used alkali metal alkoxides and hydroxide reagents. In the presence of 1,8-diazabicyclo [5.4.1]undec-7-ene (DBU), the reaction of α-substituted cyclopentanones **21** with α,β-unsaturated aldehydes in acetone or toluene yielded polysubtituted 2-hydroxybicyclo[3.2.1]octan-8-ones **22** (equation 15 in Scheme 7).[11a] The choice of substrates and solvents had a dramatic effect on the formation of final products. The use of simple cyclic β-ketoesters and 2-substituted acroleins in methanol delivered the functionalized seven-membered rings **23**. The overall transformation involved a conjugate addition, an intramolecular aldol condensation, a retro-Dieckmann reaction followed by dehydration, and chemoselective ester saponification (equation 16 in Scheme 7).[11b] The sequential conjugate addition/intramolecular aldolization for the construction of bicyclo[3.3.1]nonanes was developed by Yamamoto and coworkers. Under the catalysis of tetrabutylammonium flouride (TBAF) or piperidine, the reaction of dimethyl 1,3-acetonedicarboxylate and enals proceeded smoothly in THF at room temperature, giving the corresponding sequential products **24** in 53–99% yields (equation 17 in Scheme 7).[11c] Some bicyclo[3.3.1]nonanes have had many important applications and properties.[11d,e] Furthermore, the formation of optically active bicyclo[3.3.1]nonanes has recently been achieved by using chiral organocatalysts.[11f]



Scheme 7

The easily accessible nonionic phosphazene base or 4-(dialkylamino)pyridines proved to be efficient catalysts for the conjugate addition of β-ketoesters in water at room temperature. The reaction with a series of electron-deficient acceptors resulted in high-yield conversion to the corresponding adducts **25** (equation 18 in Scheme 8).[12a,b] In the presence of benzyltrimethylammonium hydroxide (Triton B), the addition of dimethyl propargylmalonate **26** to nitroalkenes offered a method for the diastereoselective synthesis of nitro methylenecyclopentanes **27** (equation 19 in Scheme 8).[12c] Under the catalysis of triethylamine or diisopropylethylamine (DIPEA), the addition reaction of ethyl 4,4,4-trifluoro-3-oxobutanoate and 4-hydroxy-*N*-methylquinolinone to β-nitrostyrenes gave the fluorine-containing furan derivatives **28** and hydroxyiminodihydrofuroquinolinones **29**, respectively (equations 20 and 21 in Scheme 8).[12d,e]

Treatment of 1,3-dicarbonyl compound **30** and nitroalkene with achiral base 1,4-diazabicyclo[2.2.2.]octane (DABCO) in toluene led to the formation of two of the possible four diastereoisomers, **31a** and **31b**, in a 4.3: 1 ratio, respectively (equation 22 in Scheme 9).[13a–c] To improve diastereoselectivity, bifunctional cinchon-derived organocatalyst was introduced to facilitate the conjugate addition and the major diastereoisomer **31a** was obtained in 80% yield. The application of this addition reaction has been demonstrated as a key step for the synthesis of marine alkaloid (−)-nakadomarin A. A DBU-catalyzed tandem conjugate



Scheme 8

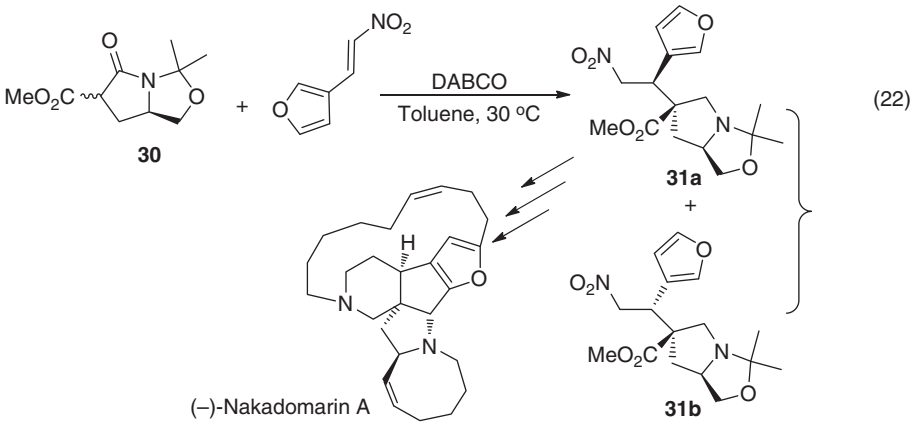
addition of 2-aminomalonates to electron-deficient 1,3-conjugated enynes **32** was realized under mild conditions. A wide range of conjugated enynes was employed to afford highly functional 2-pyrroline derivatives **33** (equation 23 in Scheme 9).[13d]

Whether under conventional heating or microwave irradiation (MWI), the conjugate additions of cyclic 1,3-dicarbonyl compounds **34a** and **34b** to the same electron-deficient acceptors in the presence of DBU presented the adducts *trans*-**35a** and *cis*-**35b**, respectively (equation 24 in Scheme 9).[13e] Both transformations occurred via domino intermolecular conjugate addition/proton exchange/intramolecular displacement annulation sequence. The origin of the divergent stereochemistry of the apparently related adducts suggested that the mechanisms of formation of these products probably differ. Owing to steric and/or electronic interactions, *trans*-**35a** was generated via the displacement of the sulphonyl moiety by the oxygen of the enolate anion, whereas *cis*-**35b** was produced via that of the amide anion (Figure 2).

Recently, *N*-heterocyclic carbenes (NHCs) have also been identified as efficient organocatalysts in the conjugate addition of 1,3-dicarbonyl compounds (equation 25 in Scheme 10).[14a,b] The catalytic cycle would be initiated by the formation of enolate–imidazolium complex **36** in which the carbene plays the role of a Brønsted base in a similar manner to the methyl acetoacetate–IAd (IAd = 1,3-bis(1-adamantyl) imidazol-2-ylidene) complex reported by Nolan and coworkers.[14c] Complex **36** would then behave as a Lewis acid and activate the electrophile, as depicted in complex **37**, which would evolve to afford the conjugate adduct and regenerate the NHC.

α-Nitro carbonyl compounds are also useful substrates in many conjugate reactions. This is mainly because the proton *α* to the carbonyl group is fairly acidic and can be easily removed under mild conditions, thus permitting C–C bond formation. In this context, polyfunctionalized products can be easily prepared combining the conjugate addition process with other transformations in one-pot sequential procedures. Conjugate addition of 2-nitrocycloalkanones with enones afforded adducts **38**, which were reduced with $NaBH_4$ in acetonitrile-water via a retro-Claisen cleavage, producing hydroxynitronate **39** as an intermediate. On acidification of the reaction mixture, both Nef reaction and spontaneous cyclization occurred to give spiroketals **40** (equation 26 in Scheme 11).[15a] In the presence (or absence) of Ph_3P, the addition of 2-nitrocycloalkanones with *α,β*-unsaturated carbonyl acceptors proceeded under mild conditions to give 1,5-dicarbonyl derivatives **41** (equation 27 in Scheme 11).[15b–f] A retro-Claisen cleavage of the 2-nitrocycloalkanones **41** could be realized under basic conditions to afford open-chain nitronates **42**. Treatment of **42** in reductive conditions chemoselectively furnished *cis*-pyrrolidine **43**,[15b] whereas further oxidation led to the formation of trioxo derivatives **44**.[15c]

In aqueous base, the use of 2-nitrocycloalkanones and *α*-alkyl-*α,β*-unsaturated aldehydes led to the one-pot synthesis of functionalized medium-sized lactones or macrolactones **45** (equation 28 in Scheme 12).[16a,b] In this domino transformation, cyclization of open-chain nitronate anion would lead to the *N*-oxide. Further elimination of water and an intramolecular



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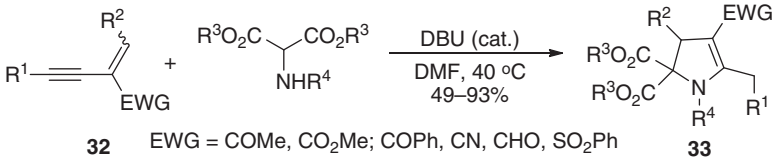

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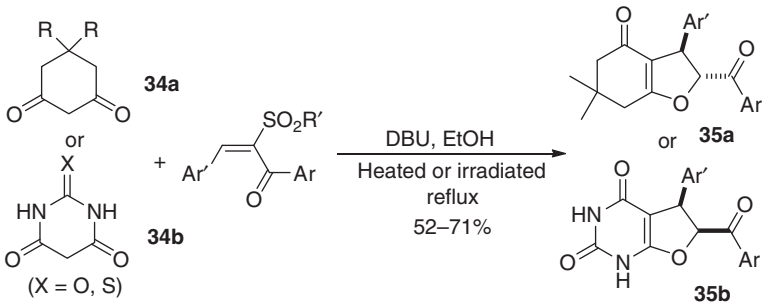


(24)

Scheme 9

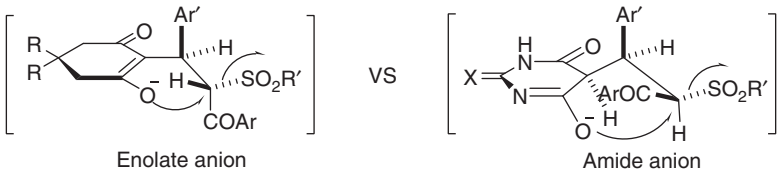
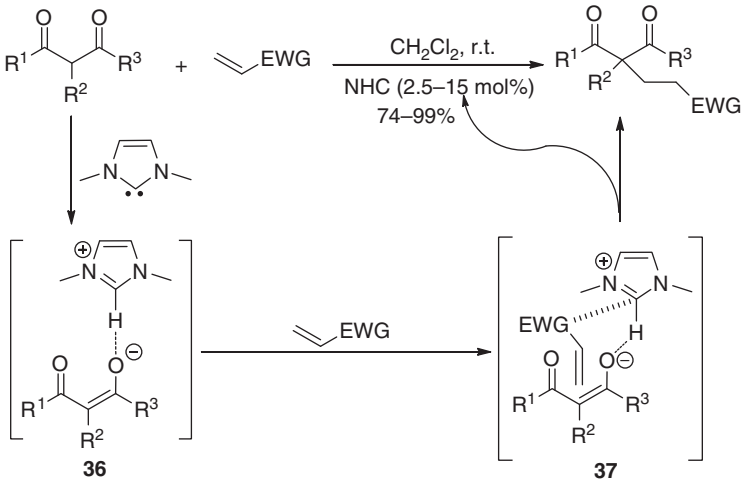


Figure 2 The mechanisms of formation of *trans*-**35a** and *cis*-**35b**.

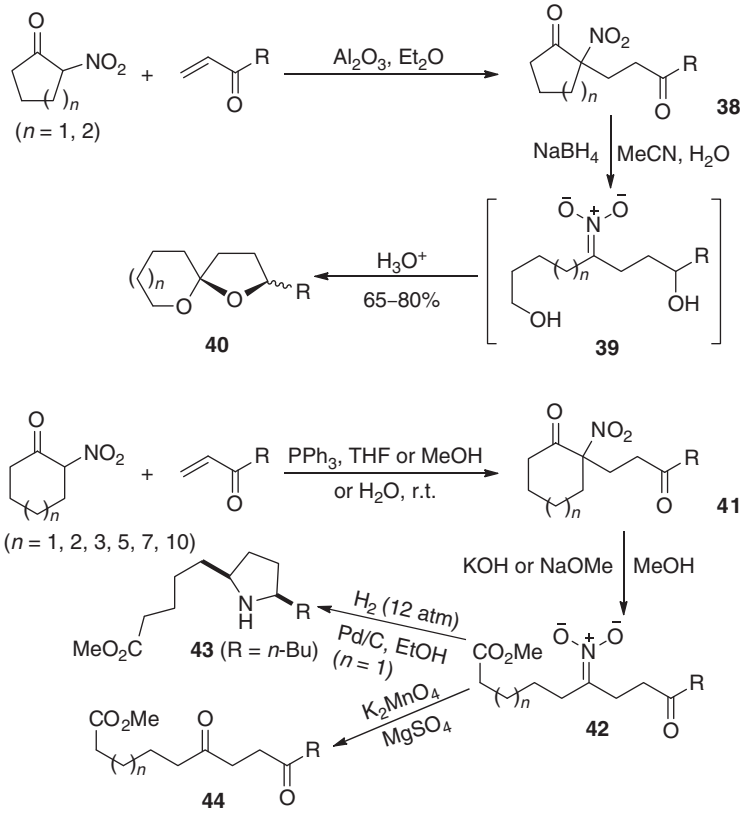
conjugate addition of the carboxylate group onto the α,β-unsaturated imine system led to the formation of the observed products. Starting from similar materials, a base-promoted Michael–aldol anionic domino reaction was also developed to afford bicyclo [*n*.3.1]alkanone systems **46** in 30–100% yields (equation 29 in Scheme 12).[16c,d] This domino reaction generates up to four stereocenters, three of which are contiguous, including a functionalized bridgehead quaternary carbon atom.

Stable isotope-labeled L-glutamic acid can be prepared from ^{13}C-enriched compounds following a strategy involving the conjugate addition of ethyl nitroacetate to ethyl acrylate. Oxidative Nef conversion of the adduct **47** to diethyl 2-oxoglutarate and ester hydrolysis gave 2-oxoglutaric acid **48**. This diacid was transformed into L-glutamic acid **49** using the commercially available enzyme glutamic dehydrogenase in the presence of ammonium ions (equation 30 in Scheme 13).[17a] The conjugate addition of ethyl nitroacetate with 2-bromoenones gave the intermediate adducts **50**, which underwent an intramolecular nucleophilic substitution involving the oxygen of the nitronate anion and the bromine atom. The reaction could be realized in homogeneous (Et_3N, ether) as well as heterogeneous conditions (basic alumina), and the 2-isoxazolines **51** are formed predominantly as *trans* isomers (equation 31 in Scheme 13).[17b] 2-Nitro esters and amides reacted with allyl acrylate in the presence of potassium fluoride



(25)

Scheme 10



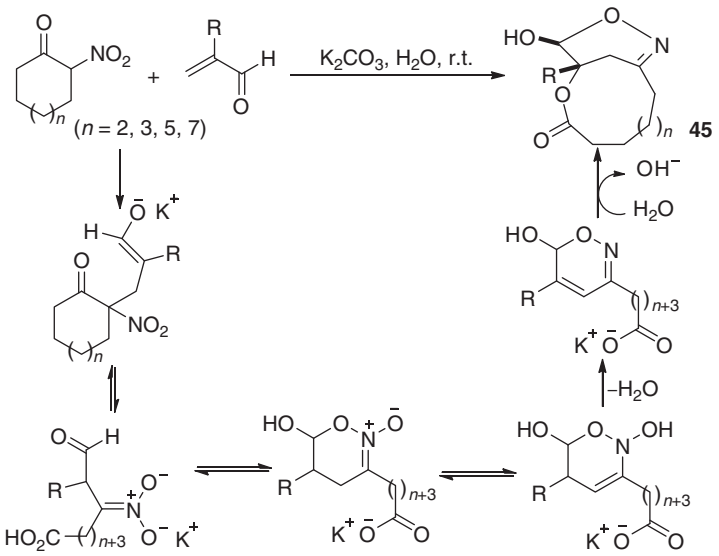
(26)

(27)

Scheme 11

(KF) to give the adducts **52** (equation 32 in Scheme 13).[17c,d] Intramolecular Pd(0)-catalyzed allyl alkylation of **52** afforded acids **53**, which could be transformed into hydroxamic acids **54** by carefully controlled reduction conditions.[17d]

In the presence of diethylamine, the conjugate addition of ethyl 2-nitroacetate with chalcones occurred to give the adducts **55** (equation 33 in Scheme 14).[18a] Reduction cyclization of the adducts **55** with formamidinesulfinic acid provided the ester-substituted diarylpyrroles **56**, which were employed as potential fluorescent sensors. Trogu et al. demonstrated that the reactions between ethyl 2-nitroacetate and electron-deficient alkenes can be modulated by use of different conditions and catalytic systems (bases of various strength, presence of Cu(II) salt) to cause either the well-known conjugate additions to give the adducts **57** or cycloaddition-condensations to afford isoxazole derivatives **58** with involvement of the nitro groups (equation 34 in Scheme 14).[18b] The conjugate additions in most cases require strong bases such as DBU and DABCO, whereas with weaker bases



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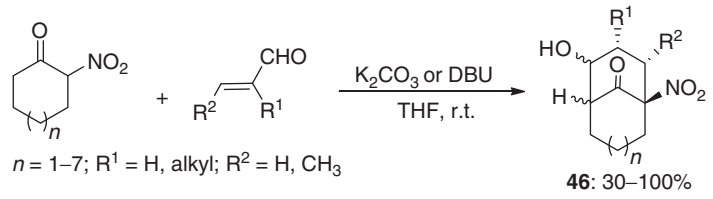


(29)

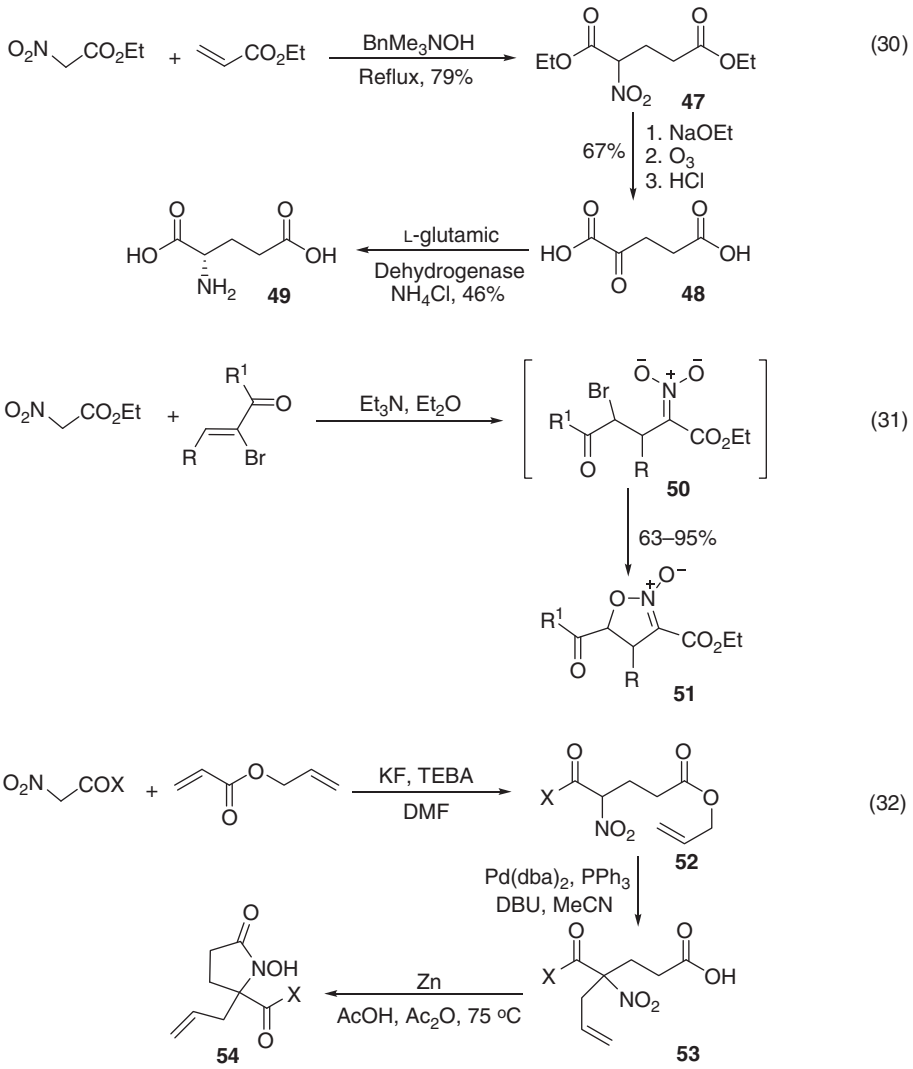
Scheme 12

the cycloaddition-condensations might be faster but take place after long induction times; addition of Cu(II) greatly reduces induction times, thus favoring the cycloaddition-condensations.

Apart from the use of various liquid or solid bases in the conjugate additions of α-cyanoacetates and their related compounds, transition metal α-cyanocarbonions have attracted much attention as active species under neutral and mild conditions (equation 35 in Scheme 15). The commonly used metal complexes include ruthenium(II),[19] rhodium(III),[20a–d] and rhenium(I)[20e,f] complexes. In these catalysts enhanced nucleophilicity of the enolato moiety by the zwitterionic structure was considered to be responsible for the driving force of the carbon–carbon bond formations. The catalytic cycle of ruthenium(II) complex has been suggested by Naota et al. (equation 36 in Scheme 15).[19h] Direct ionic addition of *N*-bound α-cyanocarbonion complex **59** to electron-deficient acceptor **60** and a subsequent 1,3-hydrogen shift afforded complex **61**, which underwent a rate-determining process of ligand exchange with nucleophilic reagent **62** to form the adduct **63** and regenerated *N*-bound α-cyanocarbanion complex **59**.

Isocyanoacetates and their derivatives, containing an acidic CH fragment, are widely used in the conjugate additons.[21] The formation of bis-adducts is a serious issue, and becomes the main process when isocyanoacetate is treated with an excess of electron-deficient acceptors in the presence of the base (equation 37 in Scheme 16). However, α-substituted isocyanoacetates react with all types of activated alkenes to form monoadducts in good yields. In addition, the more sterically hindered *tert*-butyl isocyanoacetates or the less acidic isocyanoacetamides favor monoaddition. For activated alkenes, with good leaving groups, such as nitroolefins, α,β-unsaturated sulfones, and sulfides, the initially formed Michael adducts spontaneously cyclized to form pyrroles **64** as the single product (referred to as Barton–Zard reaction) (equation 38 in Scheme 16).[21b,c]

Ito and coworkers found that the Michael reaction of α-isocyanoesters with α,β-unsaturated carbonyl compounds can be efficiently promoted by a catalytic amount of tetrabutylammonium fluoride (TBAF) to produce α-isocyano-δ-ketoesters **65** in high yields.[22a] In addition, the same group found a remarkable acceleration of the Michael reaction by employing *N*,*O*-bis(trimethylsilyl)acetamide (BSA) to give silyl enolates **66** under mild conditions. Activation of the isocyanide group through coordination by a Lewis acid promotes a nucleophilic cyclization to afford pyrroline-2-carboxylic acid derivatives **67** (equation 39 in Scheme 17).[22b] Ono's group described another interesting cyclization. The reaction of 1-diethylamino-2-nitroalkenes **68** (containing a good leaving group in the β-position) with ethyl isocyanoacetate in the presence of DBU at room temperature followed by quenching with HCl leads to 1-hydroxypyrazoles **69** in good yield (equation 40 in Scheme 17).[22c] The mechanism of this transformation is not entirely understood; however, it probably proceeds via the Michael addition intermediate. The Michael/cyclization reaction of methyl isocyanoacetate with activated alkenes catalyzed by silver acetate gave pyrrolines **70** in good yields.

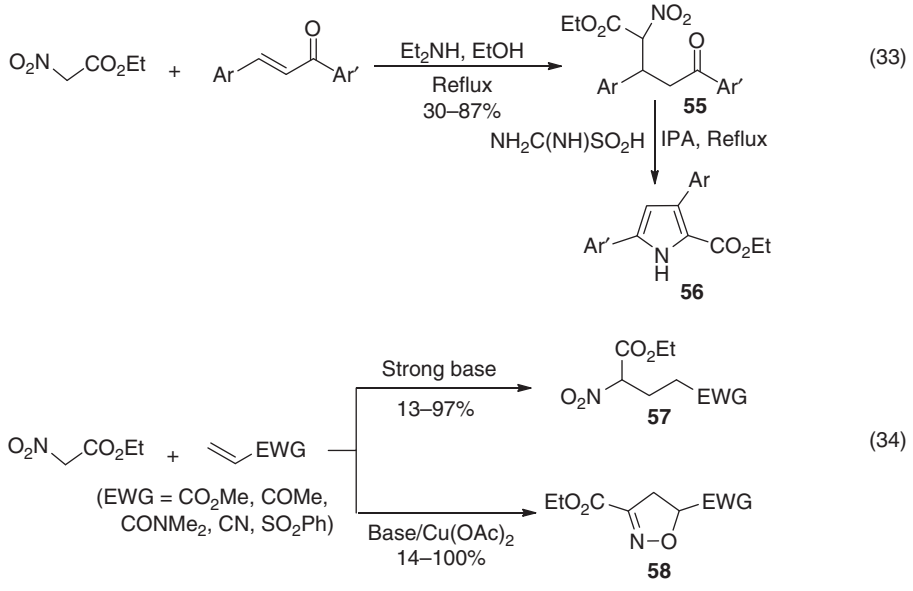


(30)

(31)

(32)

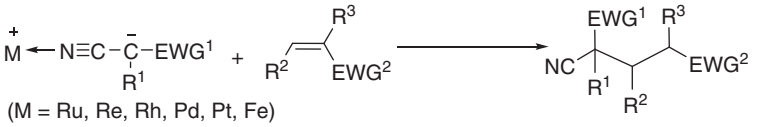
Scheme 13



(33)

(34)

Scheme 14



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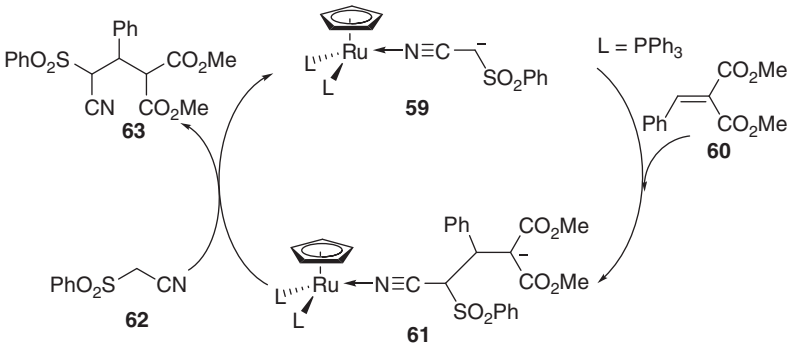
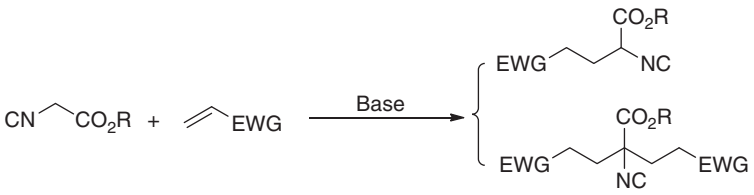


(36)

Scheme 15



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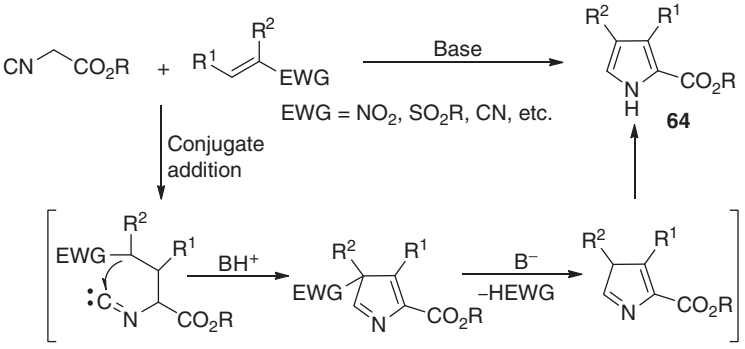
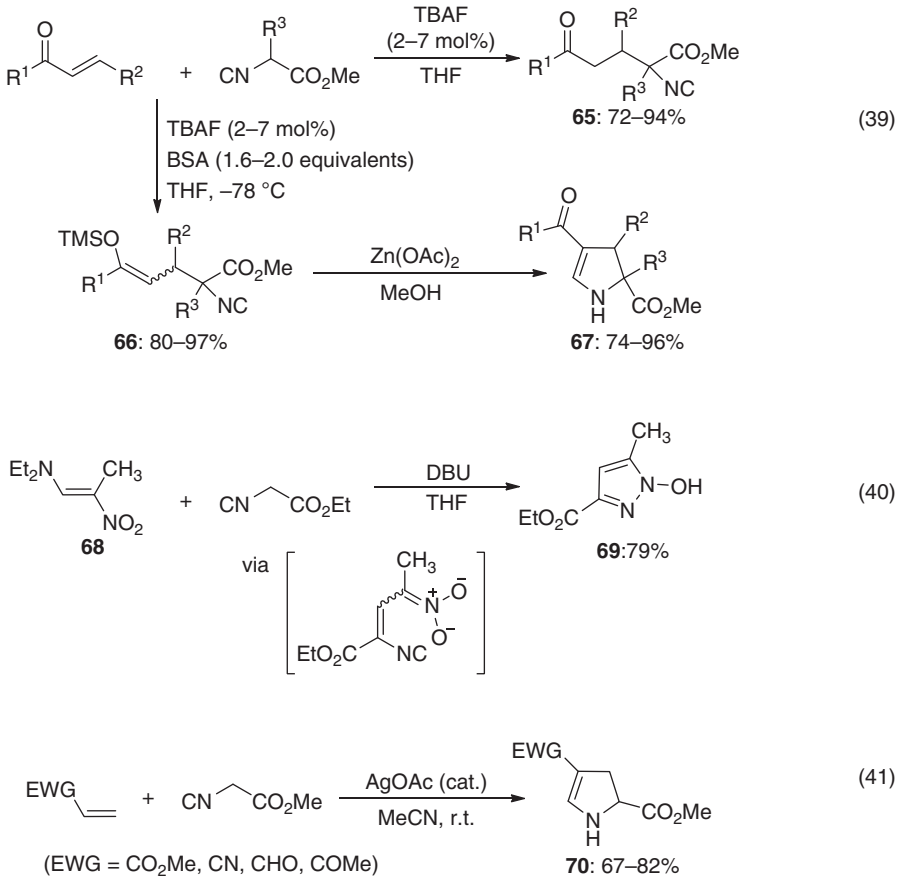


(38)

Scheme 16

This Ag-catalyzed reaction proceeded smoothly with acrylates, acrylonitriles, α,β-unsaturated aldehydes, and ketones (equation 41 in Scheme 17).[22d]

Xu and coworkers demonstrated that α-cyano-divinylketones **71** and ethyl isocyanoacetate underwent a tandem double-Michael addition/cyclization/acyl migration sequence. The reaction afforded pyrrolizidine derivatives **72** in good yields with formation of one C–N and three C–C bonds in a regio- and diastereoselective manner. The overall process involves an intermolecular Michael addition and an intramolecular Michael addition to provide the addition intermediate, which undergoes an intramolecular cyclization and a transannular attack of the imine nitrogen atom to the carbonyl atom followed by breaking of the C–C bond to give pyrrolizidines **72** (equation 42 in Scheme 18).[23a] Insertion of additional functional groups in the molecule of divinyl ketone opens broad possibilities for tandem Michael additions or heterocyclizations. Thus, divinyl ketones **73** with a carbonyl group in the α-position can be involved in the Michael addition/intramolecular [3+2] isocyanide cycloaddition reaction to give fused oxazoles **74**. The reaction takes place in a highly diastereoselective manner and yields a single diastereomer (equation 43 in Scheme 18).[23b] Subsequently, the same group also found that under the catalysis of DBU, isocyanoacetate reacted with divinyl ketones **75** to produce 1-amino-cyclohexanecarboxylic acid derivatives **76**. This reaction proceeded in a diastereoselective manner forming only one diastereomer of double-Michael adducts **76** (equation 44 in Scheme 18).[23c]



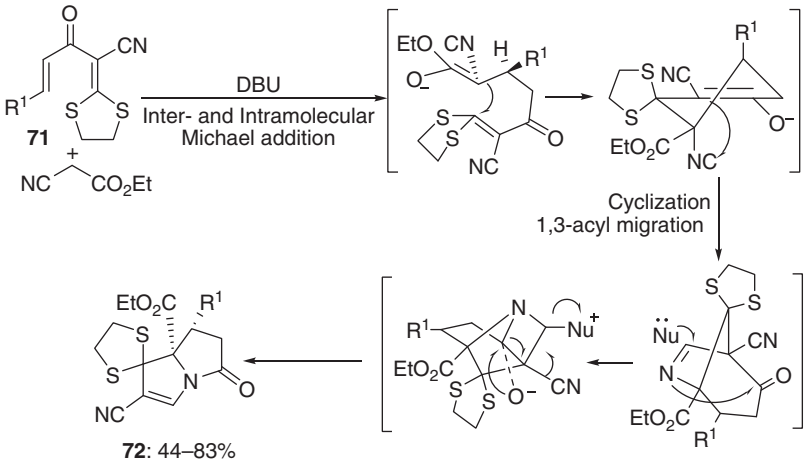
Scheme 17

The glycine-derived aldimines and ketimines have been widely used as glycine anion equivalent in the synthesis of amino acids. From the first publication about these compounds in 1978,[24] many efficient tansformations have been developed from these readily available strarting materials. In the conjugate addition of glycine imines, acrylates, arylamides, unsaturated nitriles, vinyl aryl sulfones, linear and cyclic unsaturated carbonyl compounds, and nitroalkenes have been applied as Michael acceptors. The earlier studies in this area focused on the use of strong bases under relatively harsh reaction conditions. For example, Rowley et al. reported the addition of glycine imine to nitrostyrene mediated by lithium diisopropylamide (LDA) and the application of the adduct **77** in the synthesis of 4-substituted analog **78** of the glycine/*N*-methyl D-aspartate antagonist HA-966 (equation 45 in Scheme 19).[25a] In 1994, Zindel and DeMeijere described *n*-BuLi-mediated tandem Michael addition/intramolecular substitution of glycine imine with 3-bromo-1-niroalkene for the preparation of cyclopropyl-containing amino acids **79** (equation 46 in Scheme 19).[25b]

Considering the air and moisture sensitivity of the strong bases used and the low reaction temperature, many groups paid more attention to the mild conjugate additions of glycine imines. By using quatenary ammonium salts, both Spanish groups developed the phase-transfer-catalyzed conjugate additions of the enolates glycine imines with α,β-unsaturated carbonyl compounds for the highly diastereoselective synthesis of substituted glutamic acids **80** (equation 47 in Scheme 20).[26a,b] Good chemical and optical yields can be obtained by the catalysis of chiral quatemary ammonium salts derived from natural alkaloids or other chiral sources. Selective removal of the protecting group with concomitant cyclization gave rise to polyfunctional proline derivatives with retention of configuration.[26d–f] Tzalis and Knochel found that tris(polypyridyl)ruthenium(II) complexes **81** could also be employed as phase-transfer catalysts in the conjugate addition of the enolates glycine imines with α,β-unsaturated carbonyl compounds (equation 48 in Scheme 20). These Ru-complexes can be easily recovered and reused without any significant loss of activity.[26c] Recently, Du and coworkers described a mild conjugate addition of glycine imines to aromatic nitroalkenes under the catalysis of DBU and LiOTf. In most cases, the *syn*-adducts **82a** could be obtained as major diastereomers (equation 49 in Scheme 20). However, the selectivity for *syn*-adduct can be reversed to *anti*-**82b** when the R group of glycine imines is changed from methyl or ethyl to *tert*-butyl.[26g]

4.01.2.1.1.2 Aldehydes, ketones, and esters

Since enols or enolates of aldehydes may also attack the carbonyl group directly (aldol reaction), the direct conjugate additions of naked aldehydes are rare.[27] Hagiwara et al. presented the first example of conjugate addition of naked aldehydes to electron-deficient



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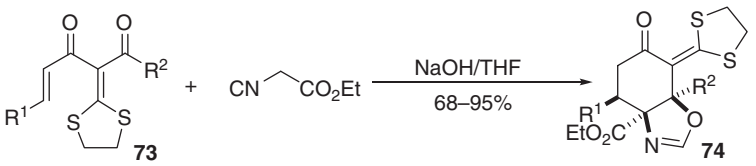

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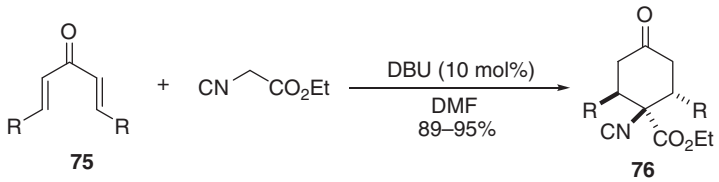

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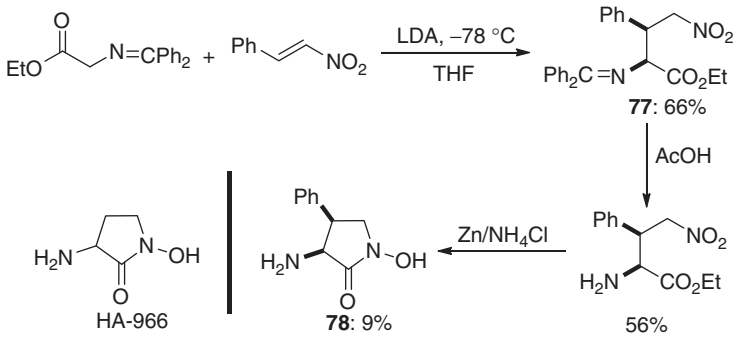
Scheme 18



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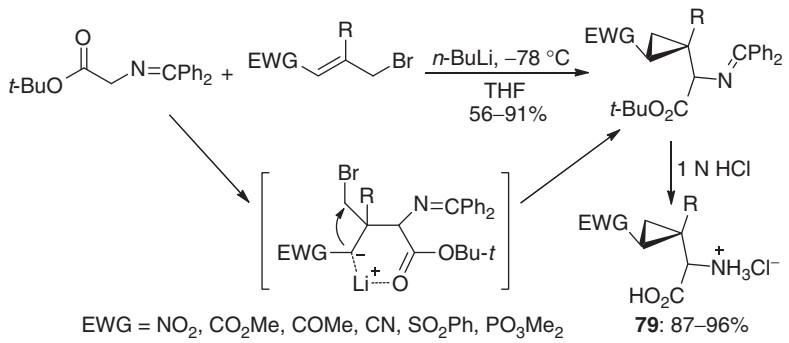
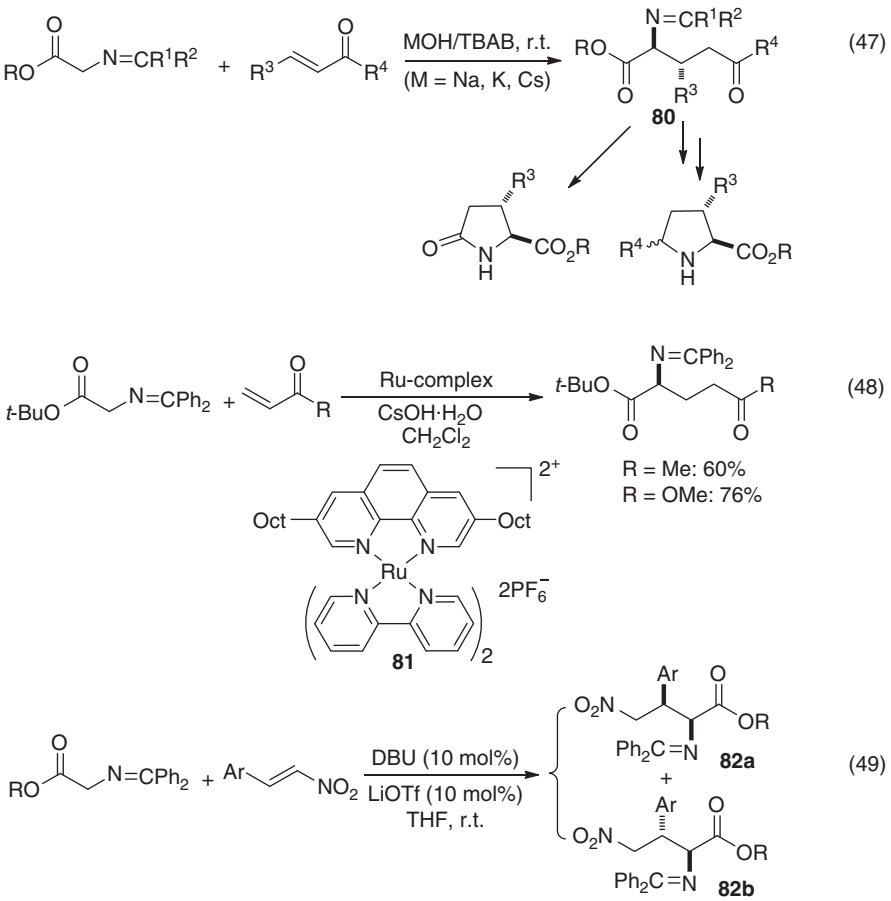


(46)

Scheme 19



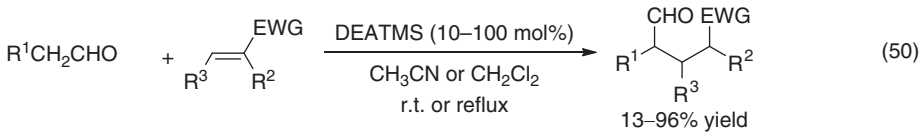
Scheme 20

olefins by using diethylamino(trimethyl)silane (DEATMS) (equations 50 and 51 in Scheme 21).[28] The condition mildness was well exemplified by the successful results of the reaction with a series of acid- or base-sensitive aldehydes. Reaction of aldehydes with α-methylenecycloalkanones generated *in situ* from the corresponding mesyl ester and DEATMS provided a mixture of 5-keto aldehyde diastereomers **83** in good yield irrespective of ring size. With this conjugate addition reaction as the key step, natural product α-Bisabol-1-one was obtained in 78% overall yield (equation 52 in Scheme 21).[28d] In addition, treatment of naked aldehydes and α-halo-α,β-unsaturated esters with DEATMS in acetonitrile furnished formylcyclopropanecarboxylate **84** via the tandem conjugate addition/substitution process. The tandem product was a mixture of diastereomers in which major isomer bears *syn* stereochemistry referring to the formyl and ester groups (equation 53 in Scheme 21).[28a]

This conjugate addition pathway was proposed to proceed via a diethylaminoenamine intermediate, which generated *in situ* from DEATMS and aldehydes. Fair instability of the diethylaminoenamine might play an important role in driving the reaction forward (equation 55 in Scheme 21). It is noteworthy that diethylamine also directly promoted the conjugate addition of naked aldehydes to MVK (equation 54 in Scheme 21).[28c] These experimental results provided further supportive evidence of enamine mechanism. The same group also immobilized *N*-methylamino residue on amorphous silica (NMAP-SiO_2) or FSM-16 (NMAP-FSM), which led to conjugate adducts in comparable yield.[28e] Furthermore, it was found that conjugate addition reaction of naked aldehydes proceeded efficiently in highly polar ionic liquid [bmim]PF_6. Employing NMAP-SiO_2, not only ionic liquid but also the catalyst was recycled intact four times in moderate yields (46–59% yield) without any further treatment to reactivate the catalyst after the reaction.[28f,g] Today, the efficiency and scope of enamine catalysis, and particularly asymmetric catalysis, have been well established. Many reviews have summarized the related advances of enamine catalysis.

An alternative method was devised by the Na-mediated isomerization of allylamine leading to aldehyde enamine, though the process is not generally applicable to various substrates. The reaction of the sodium anion of (*S*)-*N*-(α-methylbenzyl)allylamine **86** formed *in situ* with 2 equivalents of *tert*-butyl cinnamate, via a tandem conjugate addition/Michael addition/ring-closure sequence, led to the formation of aminocyclohexane **87** containing six new stereogenic centers in 44% yield (equation 56 in Scheme 22).[29]

The generation and use of keto-enamines and enol ether is well established in organic synthesis.[30] Willis et al. described palladium complex-catalyzed cross-coupling of vinyl halides/triflate with pyrrolidine to afford enamine intermediates, which were treated *in situ* with alkylidene malonates to produce conjugate adducts **88** (equation 57 in Scheme 23),[31a] whereas Ricci and



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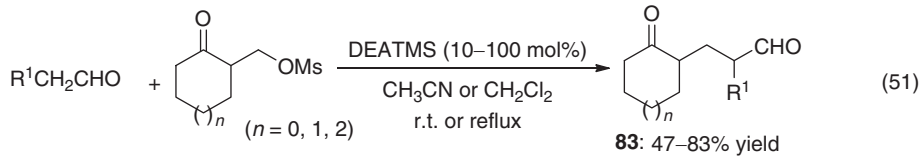

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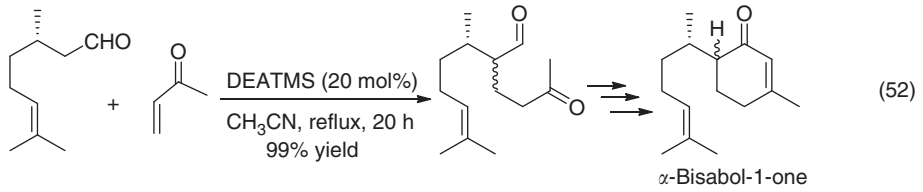

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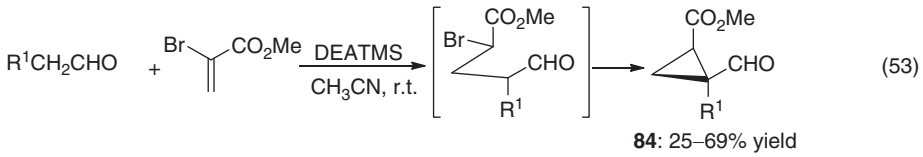

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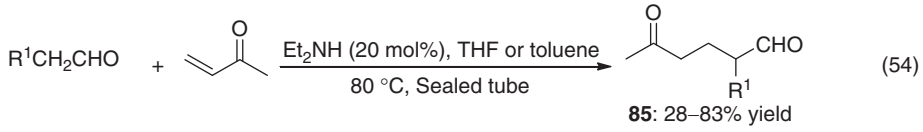

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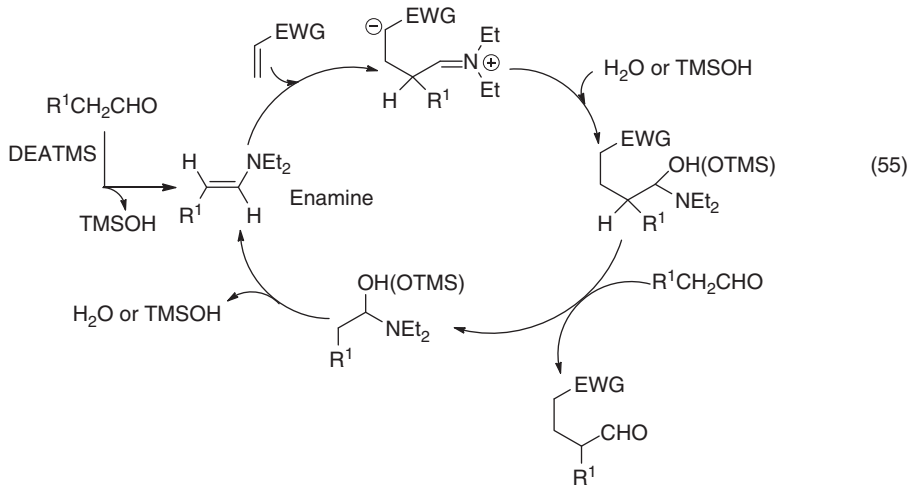
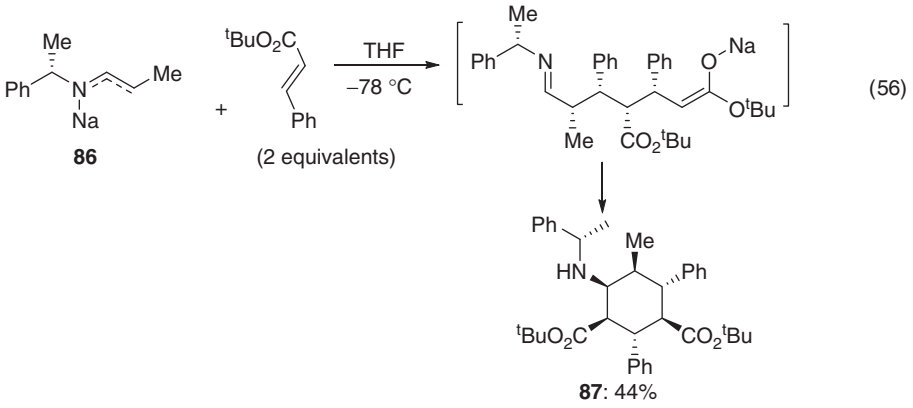


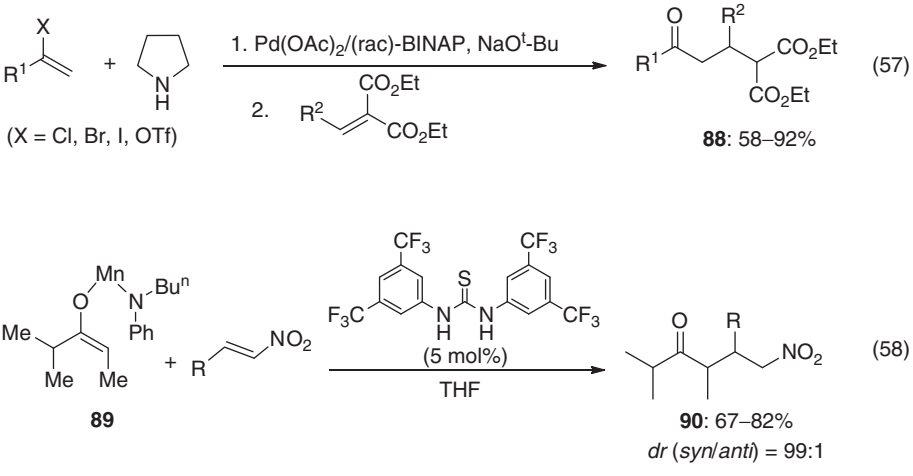
(55)

Scheme 21

coworkers reported a Michael addition of nitroolefins with manganese enolates **89** derived from an array of ketones. The desired conjugate adducts **90** were obtained with excellent diastereo- and regioselectivity (equation 58 in Scheme 23).[31b] Using the kinetically generated enolate from 1,3-cyclohexanedione enol ethers, Inokuchi's group presented a facile conjugate addition to *β*-nitrostyrenes, giving the adducts **91** installed with a two-carbon chain and a nitrogen function in good yields. In this addition, the adducts were obtained as a mixture of diastereomers at the C6 in a six-membered ring and arylalkyl carbon of the side chain with no selectivity (*c.* 1:1). However, the stereochemistry would be thoroughly erased in the next step, and hence adducts **91** were transformed without separation of two isomers to construct polysubstituted 6-alkoxyindoles (equation 59 in Scheme 23).[31c]



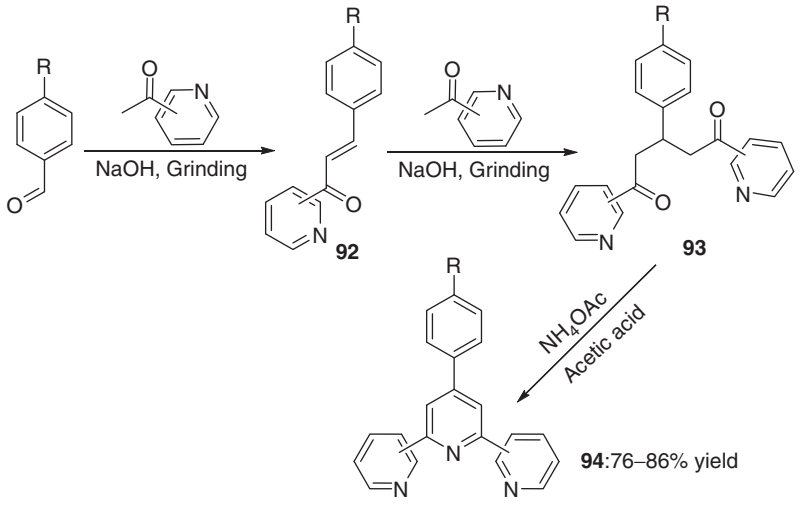
Scheme 22



Scheme 23

The grinding of 2-acetylpyridine and 4-substituted benzaldehydes with NaOH in neat gave the corresponding condensation enones **92**, which could act as Michael acceptors to react with another 2-acetylpyridine in one pot. The formation of enones **92** and adducts **93** is essentially quantitative and subsequently does not require isolation from the reaction mixture before the tertiary step whereby the diketone was consequently treated with ammonium acetate in acetic acid to generate the terpyridyl products **94** in high yield (equation 60 in Scheme 24).[32a,b] Yanagisawa and coworkers developed a tandem cross-coupling reaction between aryl methyl ketones and aromatic aldehydes catalyzed by barium isopropoxide, in which aldol reaction, β-elimination, and conjugate addition occur sequentially. This one-pot procedure provided a convenient method to obtain symmetrical 1,5-diketones **95** in 37–78% yields (equation 61 in Scheme 24).[32c,d]

Enolates of esters and amides are very useful carbon nucleophiles in organic synthesis. Jahn demonstrated that (*Z*)-enolates generated by deprotonation of the ester with LDA–THF–HMPA underwent a useful *anti*-selective addition to Michael acceptors providing good yields of adducts **96** (77–96%, *anti*/*syn* > 4.6/1). Interestingly, the combination of this anionic conjugate addition of lithium ester enolates with radical 5-*exo* cyclizations through single electron transfer in one pot gave highly functionalized cyclopentanes **97** (equation 62 in Scheme 25).[33a] Schmidt and Kazmaier described a convenient conjugate addition of zinc-chelated glycine ester enolate to α,β-unsaturated esters. By quenching the reaction with TMSCl and heating, a subsequent



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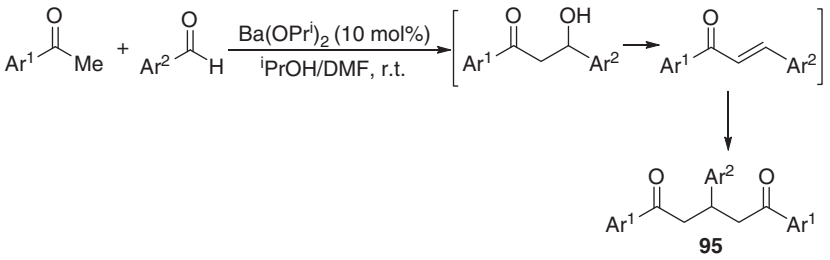
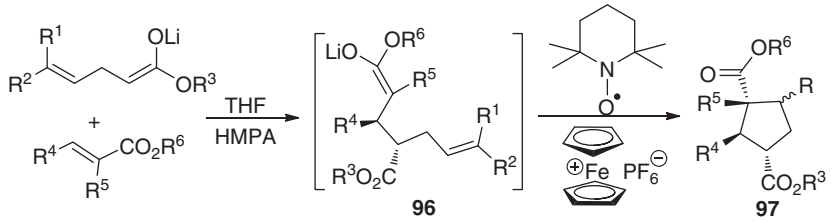


(61)

Scheme 24



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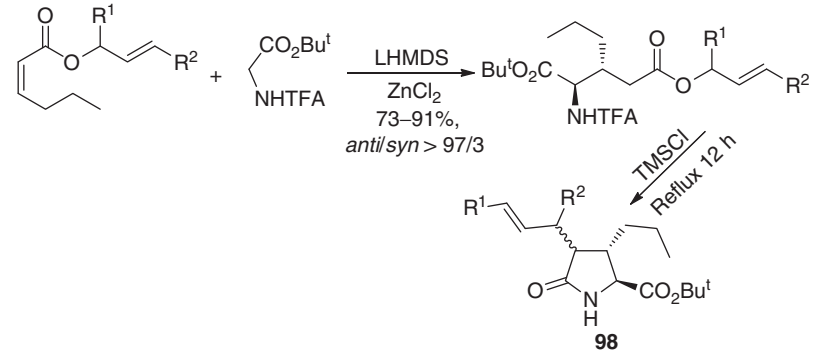
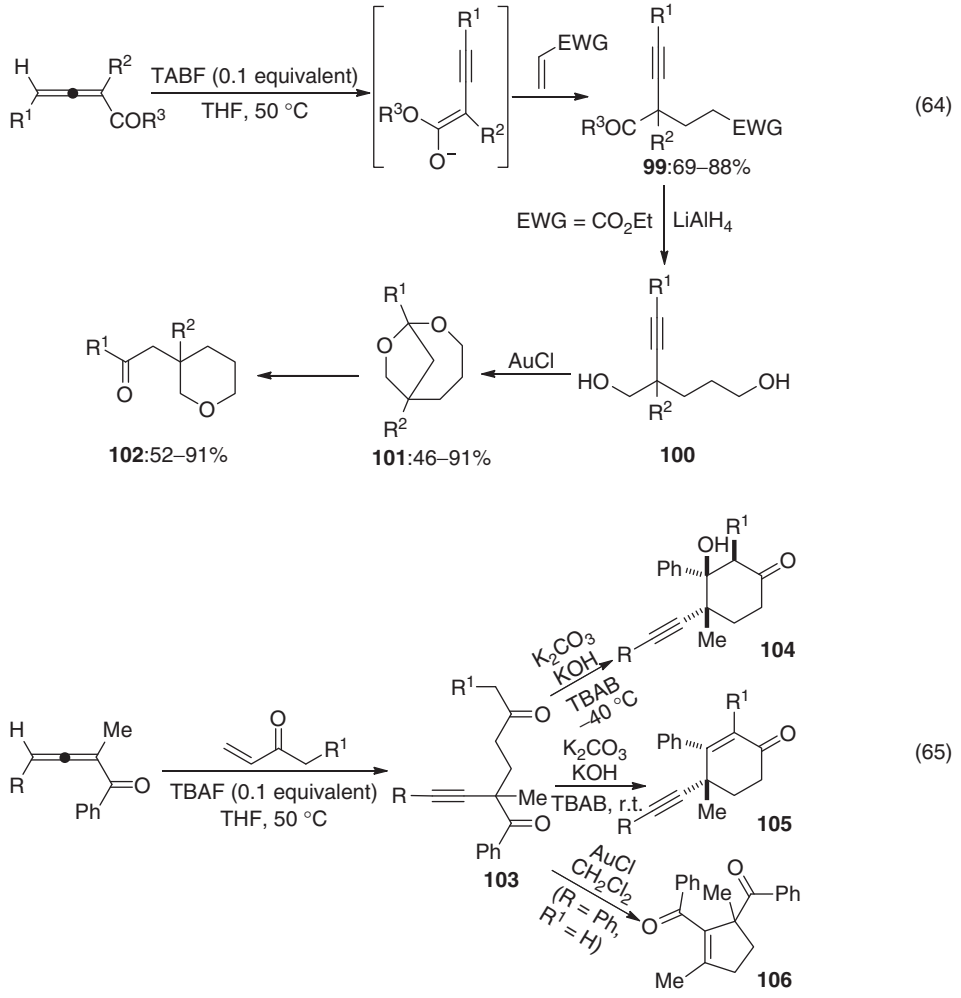


(63)

Scheme 25

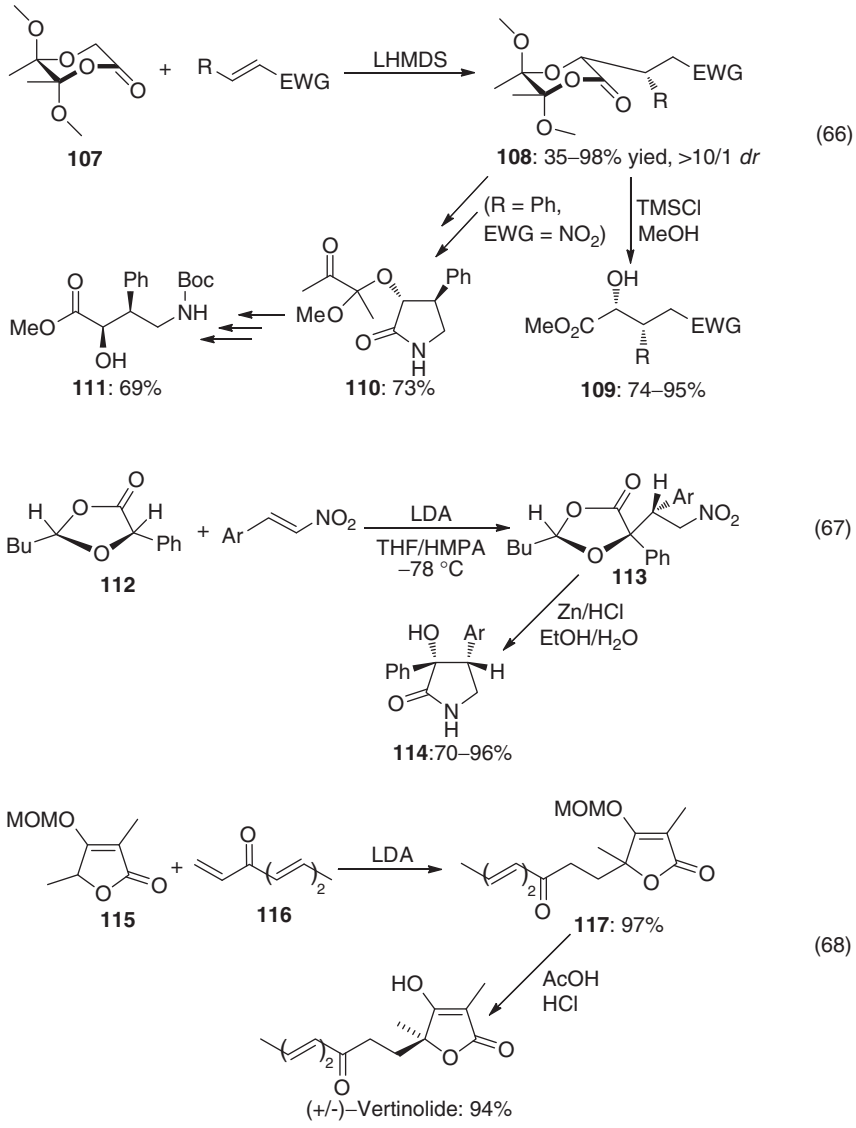
Ireland–Claisen rearrangement can occur. Direct cyclization of the rearrangement product gave rise to highly substituted pyroglutamic acid derivatives **98** (equation 63 in Scheme 25).[34b]

In the presence of TBAF, γ-proton-containing allenoates could be transformed into alkynylenolate intermediate. Hammond's group employed this alkynylenolate intermediate for the conjugate addition reaction of electron-deficient olefins to afford 2-alkynyl-substituted 1,5-dicarbonyl compounds **99** (equation 64 in Scheme 26).[34a] The adducts of 2-alkyne-1,5-dicarboxylates could be reduced into 2-alkynyl-1,5-diols **100**, which were further converted into dioxabicyclo[4.2.1] ketals **101** and tetrahydropyrans **102** via a gold(I)-catalyzed cycloisomerization reaction.[34b] 2-Alkynyl-1,5-diketones **103**, obtained from the addition of allenic ketones to vinyl ketones, could undergo an aldol reaction under the basic condition to afford 4-alkynyl-3-hydroxycyclohexanone **104** at low temperature and 4-alkynylcyclohexenones **105** at room temperature (equation 65 in Scheme 26).[34c] Furthermore, 2-alkynyl 1,5-diketone was also converted into cyclopentenyl ketones **106** under the catalysis of gold (I) chloride.[34d]



Scheme 26

The lithium enolate of butane-2,3-diacetal-desymmetrized glycolic acid **107** underwent diastereoselective conjugate additions to α,β-unsaturated ketones, lactones, and nitroolefins. Subsequent deprotection of these adducts **108** gave α-hydroxy acids **109** in high yield. Hydrogenation of the nitro group in some of the adducts leads to γ-lactams **110**, which can be easily converted into α-hydroxy-γ-amino acid derivatives **111** (equation 66 in Scheme 27).[35a] The conjugate addition of the lithium enolate of substituted lactone **112**, derived from optically active (*S*)-mandelic acid and pivalaldehyde, to several aromatic nitroalkenes in the presence of hexamethylphosphoric triamide (HMPA) proceeded to give the corresponding adducts **113** in 16–96% yields with good diastereoselectivity (up to *dr* 93/7). Reduction of the nitro group with zinc powder with concomitant intramolecular aminolysis of the acetal moiety led directly to enantioenriched α-hydroxy-α,β-diaryl-γ-lactams **114** (equation 67 in Scheme 27).[35b] In the presence of strong base, the reaction of dimethylfuran-2(5*H*)-one **115** with octa-1,4,6-triene-3-one **116** gave the adduct **117**, which was easily converted into natural compound (±)-vertinolide in high yield (equation 68 in Scheme 27).[35c]

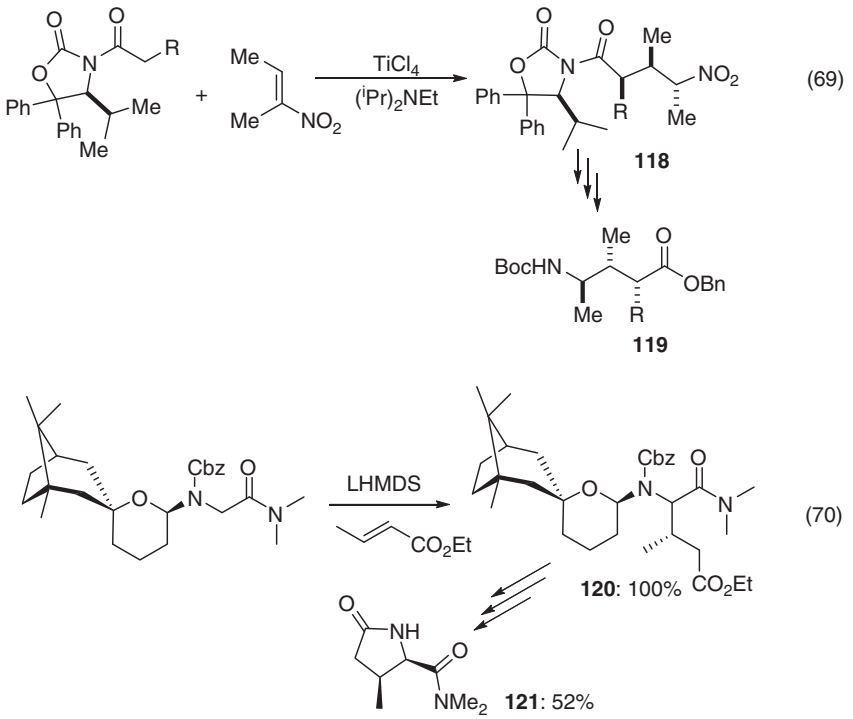


Scheme 27

Polysubstituted amino acids are important building blocks for the preparation of peptides and pharmaceutical target molecules. Seebach et al. developed a Michael addition of chiral *N*-acyl-oxazolidinone enolates with nitroolefins to diastereoselectively yield a series of adducts **118** in 50–60% yields. Subsequent reduction and deprotection led to the corresponding γ-amino acid derivatives **119** (equation 69 in Scheme 28).[36a] Dixon's group found that the lithium enolate of camphor-derived glycinamide underwent the conjugate addition to α,β-unsaturated esters to produce the adducts **120** in good yields with excellent diastereoselectivity. These adducts could be readily converted into pyroglutamic acid derivatives **121** (equation 70 in Scheme 28).[36b]

4.01.2.1.1.3 Cyanides, nitriles, and nitroalkanes

Conjugate addition of cyanides to electron-deficient alkenic acceptors has been extensively explored, which has been demonstrated to be an efficient method toward synthesis of various substituted nitriles. Barton et al. demonstrated that the addition of HCN, formed *in situ* from NaCN and HCl in solution, to a steroidal-based nitroalkene occurred in 97% yield (equation 71 in Scheme 29).[37a] This single example represents the first conjugate addition of a cyanide anion to a nitroalkene. In spite of its apparent simplicity, however, the development of this reaction is restricted by the high tendency of nitroalkenes to polymerize under basic conditions. Following Barton's research work, there are only two reports on the use of acetone-cyanohydrin and trimethylsilycyanide (TMSCN) as the cyanide source for the conjugate addition to nitroalkenes in its racemic form. One example of cyanide conjugate addition came from Anderson and coworkers, who described the one-step hydrocyanation of nitroalkenes by acetone-cyanohydrin in the presence of catalytic amounts of KCN and 18-C-6 to give β-nitronitriles (equation 72 in Scheme 29).[37b] The mechanistic study indicated that the *in situ* generated HCN, formed from the cyanide anion abstracting a proton from the



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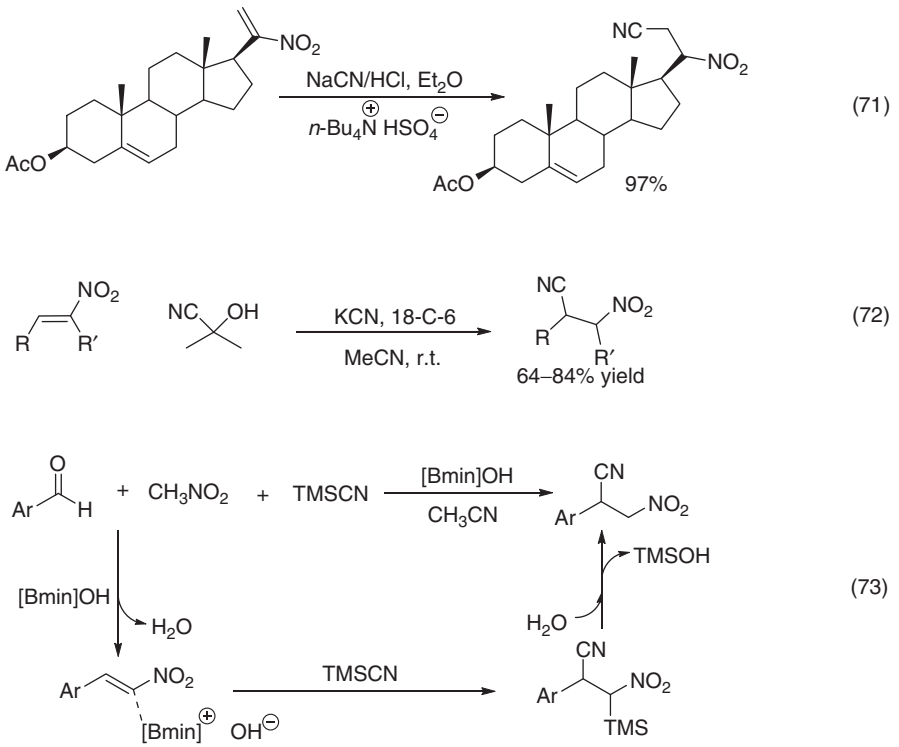
(70)

Scheme 28



(71)

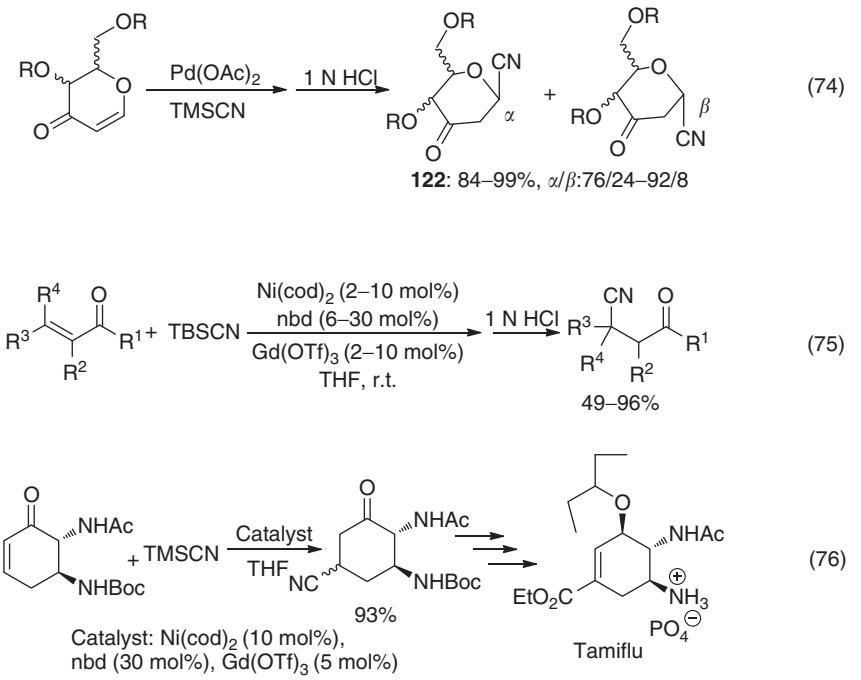
(72)

(73)

Scheme 29

acetone-cyanohydrin, was very important for the reaction to proceed. One year later, Yadav and Rai demonstrated the conjugate addition of cyanide to the *in situ* formed nitroalkenes promoted by the use of an ionic liquid (equation 73 in Scheme 29). The reaction consists of a three-component coupling of nitro methane, an aromatic aldehyde, and cyanide (in the form of TMSCN) in the presence of an ionic liquid ([bmim]OH).[37c]

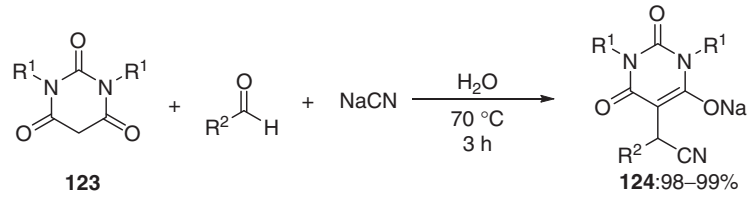
The regioselective 1,4-addition rather than 1,2-addition of weak nucleophile cyanide to α,β-unsaturated carbonyl compounds has been widely investigated. In this framework, mild cyanide sources such as HCN, NaCN, Me_3SiCN, and Et_2AlCN are frequently involved with Lewis acids.[38a–c] Some transition-metal complexes also act as efficient catalysts for the conjugate hydrocyanation of α,β-unsaturated carbonyl compounds. For example, acetylated and unprotected enones derived from D-glucal reacted with trimethylsilyl cyanide in the presence of a catalytic amount of $Pd(OAc)_2$ in 1,4-addition fashion to afford the corresponding 3-keto-glycosyl cyanides **122** in high yield and high α-selectivity (equation 74 in Scheme 30).[38d] Shibasaki and coworkers found that the cocatalysts of Ni(0) and $Gd(OTf)_3$ dramatically accelerated the conjugate addition of cyanide to enones (equation 75 in Scheme 30).[38e] The substrate scope is broad, including cyclic, linear, branched, and aromatic enones. Gadolinium triflate is supposed to facilitate the oxidative addition of Ni(0) to enones, which constitutes a key step in the catalytic cycle. The potential application of this addition reaction was demonstrated as an important step in Tamiflu synthesis (equation 76 in Scheme 30).



Scheme 30

Microwave, water, and ionic liquid have also been applied to the conjugate hydrocyanation of α,β-unsaturated carbonyl compounds in line of the concept of green chemistry. Hamana and coworkers demonstrated an efficient conjugate addition reaction of chalcones and the related enones with TMSCN under MWI.[39a] Without additive and solvent, the reactions proceed rapidly and regioselectively to give the corresponding adducts. Chen and coworkers reported a facile 1,4-addition of Me_3SiCN to enones by using CsF or Cs_2CO_3 as catalyst and H_2O as additive.[39b,c] Both aromatic and aliphatic enones are found to be suitable substrates for this protocol, and β-cyanoketones are obtained in 81–99% yield. Soleimani et al. developed a Knoevenagel condensation of barbituric acid **123** with aldehydes, followed by conjugate addition of sodium cyanide in water, producing the barbituric acid-containing nitriles or β-cyanocarbonyls **124** in up to 99% yield without using any catalyst at 70 °C (equation 77 in Scheme 31).[39d] Yadav's group presented an example of ionic liquid-promoted one-pot oxidative conjugate hydrocyanation of Baylis–Hillman (BH) adducts with TMSCN (equation 78 in Scheme 31).[39e] The oxidation of BH adducts with 2-iodoxybenzoic acid (IBX)/[bmim]Br or isomerization–oxidation with $NaNO_3$/[Hmim]HSO_4 systems afforded β-ketomethylene compounds or *E*-cinnamaldehydes. These α,β-unsaturated carbonyl compounds underwent conjugate addition with TMSCN in the same vessel to give the corresponding thermodynamically more stable β-cyanated products **125** and **126**. Thermodynamically less stable 1,2-addition products were not formed.

Nitrile anions are most often generated through the action of an appropriate base. However, the pK_a values of nitriles span a wide range – at least 20 pK_a units. Thus, the proper choice of base is usually substrate dependent. Under MWI, a DBU-promoted one-pot tandem reaction was addressed by Hu and coworkers using 3-(1-alkynyl)chromones **127** and acetonitriles as starting materials. This tandem process involves conjugate addition/cyclization/1,2-addition without a transition metal catalyst. A series of natural product-like diversified amino-substituted xanthone scaffolds **128** were constructed efficiently (equation 79 in Scheme 32).[40a] Based on this research work, the same group also developed the tandem conjugate addition/double cyclizations of 3-(1-alkynyl)chromones and 2-halobenzylic nitriles to afford functional polycyclic chromenones **129** (equation 80 in Scheme 32).[40b]



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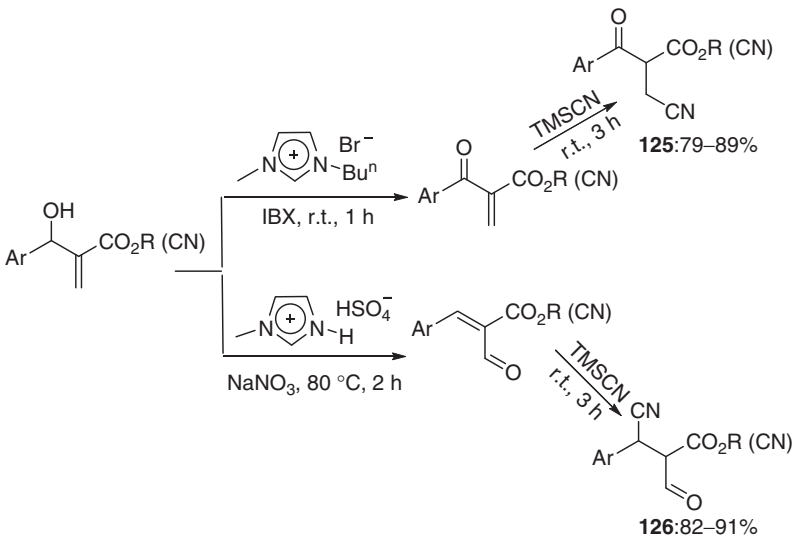

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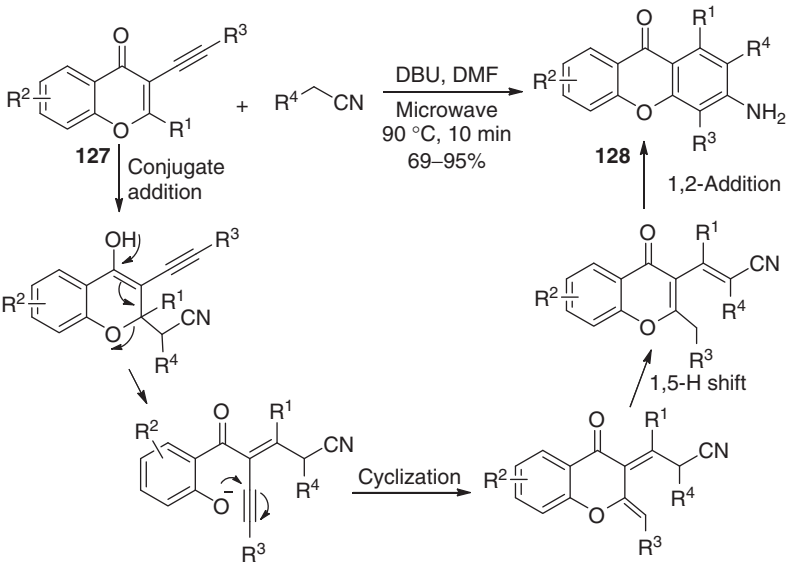
Scheme 31



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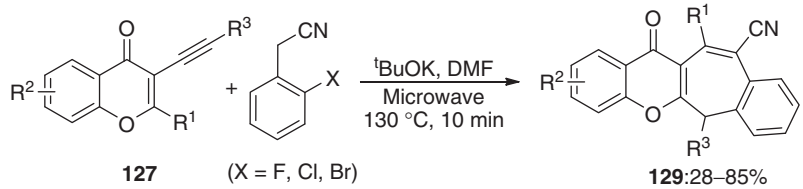
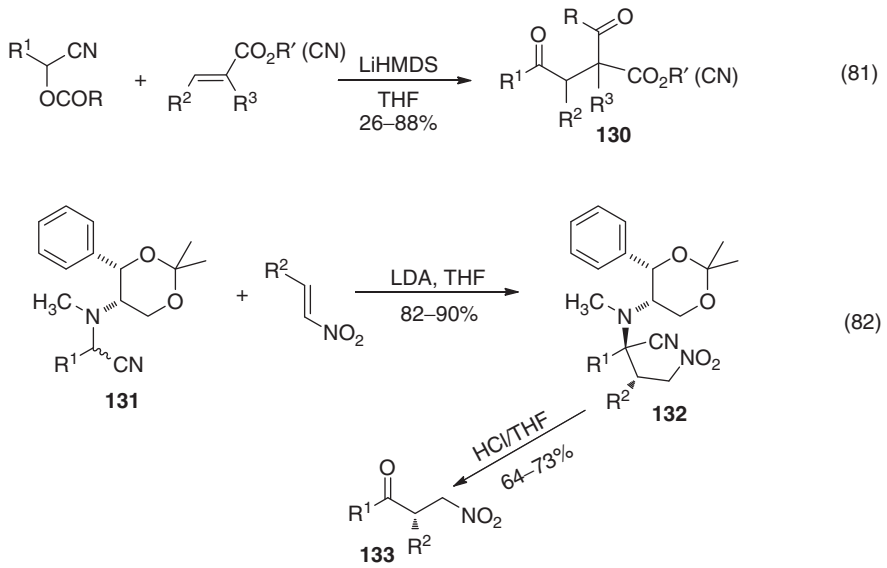


(80)

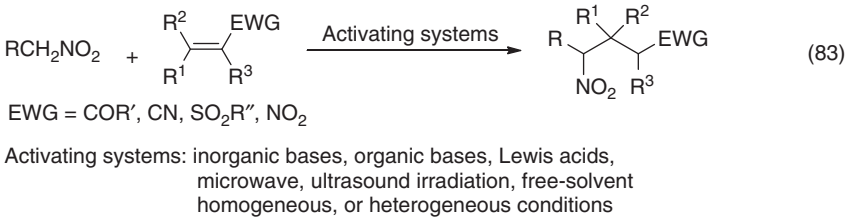
Scheme 32

The nitrile carbanions substituted by heteroatom functional groups in the α-position have been employed in intermolecular reactions as acyl carbanion equivalents. For example, acetoxy nitriles were selectively deprotonated to be added to the Michael acceptors, including acrylates, acrylonitrile, and MVK. Subsequent shift of the acyl group to the α-carbon of the Michael acceptor gave rise to the formation of diketones **130** (equation 81 in Scheme 33).[41a] The conjugate addition of lithiated α-epimeric amino nitriles **131** to aliphatic and aromatic *E*-configured nitroalkenes produced the resulting adducts **132** in good yields (82–90%), which were hydrolyzed into β-nitro ketones **133** (equation 82 in Scheme 33).[41b]



Scheme 33

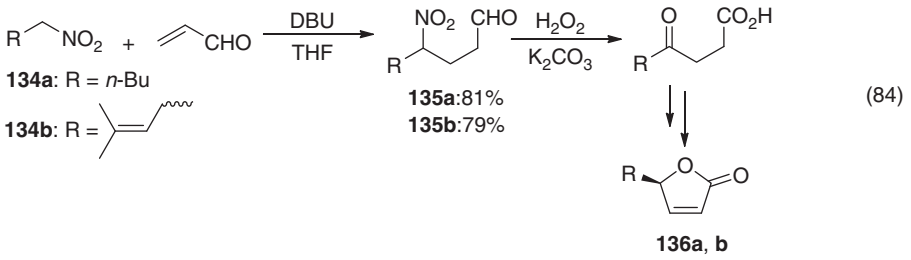
Nitroalkanes are a valuable source of stabilized carbanions since the high electron-withdrawing ability of the nitro group provides an outstanding enhancement of the hydrogen acidity at the α-position. Nitronate anions that can be generated from nitroalkanes using a wide range of bases act as carbon nucleophiles with various Michael acceptors, leading to carbon–carbon bond formation (equation 83 in Scheme 34).[42a] Over recent decades, a number of different basic systems have been introduced to carry out the conjugate addition of nitroalkanes to electron-poor alkenes.[42b–j] Most of them were just a slight modification of previously known catalysts or the use of activating techniques such as microwave and ultrasound irradiation.[43]

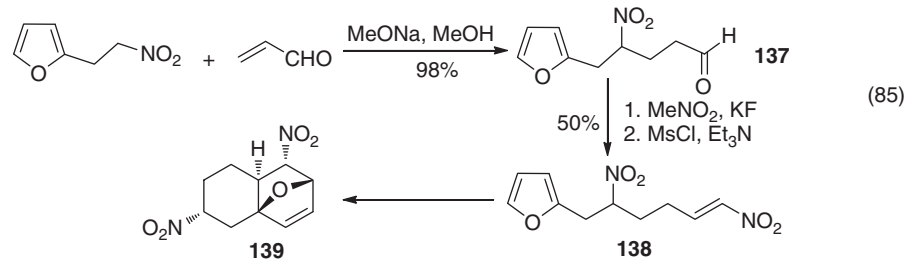


Scheme 34

The nitro group is amenable to many synthetic transformations once it has been inserted in a molecular framework.[44] This feature has favored the utilization of conjugate adducts of nitroalkanes for the preparation of various synthetic targets of practical interest. In the presence of DBU, the conjugate addition of nitroalkanes **134** to acrolein delivered the adducts **135**, which were oxidized with hydrogen peroxide to give ketoacids. Subsequent enantioselective reduction of the keto group by Baker's yeast led to lactones that were easily converted into (*R*)-*trans* whisky lactone **136a** and (+)-eldanolide **136b** (equation 84 in Scheme 35).[45a] The conjugate addition of 2-furylnitroethane to acrolein was followed by a Henry (nitroaldol) reaction/elimination of the obtained aldehyde **137** to afford nitroalkene **138**. This compound on standing at room temperature for 5 days underwent an intramolecular Diels–Alder reaction to give functionalized tricyclic derivative **139** in good yield as a single diastereomer (equation 85 in Scheme 35).[45b]

A synthetic approach to cedranoid sesquiterpene α-biotol **143** starts with a conjugate addition of nitrocyclohexene **140** to crotonaldehyde to give nitro aldehyde **141** that on reaction with isobutenylmagnesium bromide affords nitro alcohol **142**. Denitration of nitroalkanes can be easily carried out in radical conditions using Bu_3SnH/AIBN through a cascade cyclization giving





Scheme 35

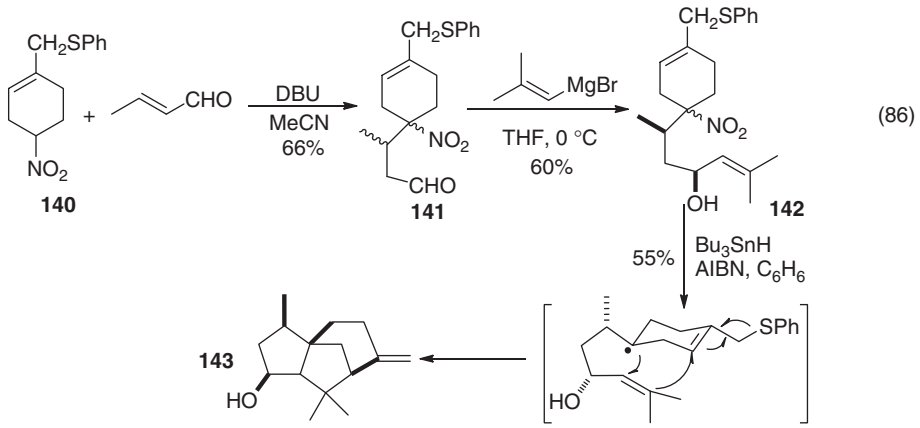
α-biotol **143** (equation 86 in Scheme 36).[46a–c] The stereochemistry of the obtained tricyclic compound **143** is totally controlled by the configuration of the carbon bearing the hydroxyl group. Nitrocyclohexitol **144** and aminocyclitol **145** can be prepared from the adducts of nitroalkanes to acrolein using an enzymatic aldol reaction followed by a highly stereoselective intramolecular nitroaldol reaction, as well as PtO_2-catalyzed hydrogenation (equation 87 in Scheme 36).[46d] Recently, Peera and Tomlinson developed a tandem conjugate addition/Henry reaction by reacting nitroalkanes with readily available α,β-unsaturated aldehydes. The dinitro compounds were further reduced by catalytic hydrogenation to obtain multifunctional diamino alcohols **146** (equation 88 in Scheme 36).[46e]

Hydroxylamines are known intermediates in the reduction of nitro compounds to amines. Reduction of the adducts between nitroalkanes and enals or enones directly produced cyclic nitrones **148** by an intramolecular reaction of the intermediate hydroxylamine **147** and the carbonyl group (equation 89 in Scheme 37).[47a–f] A three-component coupling among enals or enones, nitroalkanes, and primary amines led to the straightforward synthesis of *N*-alkylpyrroles **149** (equation 90 in Scheme 37).[47g] The reaction was carried out on solid support (SiO_2) without any solvent and was promoted by MWI. A Nef conversion of the nitro group in one of the possible intermediates of this process probably occurred, allowing the formation of the pyrrole ring through a Paal–Knorr-type reaction.[47h] Lactols **150** can be prepared by one-pot process in water, involving a sequential conjugate addition of nitroalkanes to enals or enones, reduction of the resulting γ-nitro ketone, and oxidative nitro to carbonyl conversion with concomitant cyclization (equation 91 in Scheme 37).[47i]

Allylrethrone is an important component of an insecticidal pyrethroid, and its preparation can be realized in three distinct steps, starting from the nitroalkene and MVK.[48a] The obtained conjugate adduct **151** was converted into the diketone **152** by a hydrolytic Nef reaction and was then cyclized to allylrethrone under basic conditions. Alternatively, the same process can be realized in a one-pot reaction using hydrogen peroxide to carry out the nitro to carbonyl conversion (equation 92 in Scheme 38). Double conjugate addition of nitroalkanes with enones in the presence of K_2CO_3 initially gave nitro diketone **153**, which underwent an intramolecular aldol condensation to produce 2-acyl-4-nitrocyclohexanol derivatives **154** in a diastereoselective fashion (equation 93 in Scheme 38).[48b,c] Subsequent double elimination of water and nitrous acid was carried out by refluxing of compounds **154** in toluene and bubbling air to afford dienes **155**, which were further oxidized by oxygen to the aromatic derivatives **156**. Similar double conjugate addition of nitroalkanes to divinyl ketones in the presence of DBU at room temperature gave rise to the formation of substituted cyclohexones **157**, whereas by increasing the amount of base and the reaction temperature the elimination and aromatization proceeded to furnish the substituted phenols **158** (equation 94 in Scheme 38).[48d]

The BH adduct-based esters have been successfully employed in a number of transformations leading to the synthesis of various important and useful molecules. Conjugate addition of nitroalkanes to derivatives **159** led to the expected products **160** with exclusive formation of the *E* stereoisomer (equation 95 in Scheme 39).[49a–d] The corresponding nitro esters **160** could be chemoselectively reduced by a one-pot procedure to give pyrrolidinones **161** using Fe in boiling AcOH.[49e] Further conjugate addition of the nitro esters **160** to enones or enoates and aldol-type cyclization proceeded well to afford the corresponding enols **162**, which could be converted into polysubstituted phenols **163** (equation 96 in Scheme 39).[49f]

The base used for the conjugate addition of nitroalkanes to BH derivatives may have a large influence on the related mechanistic route, and therefore the nature of the product obtained can be considerably different from that expected. The use of basic promoter DABCO involved a preliminary conjugate addition/elimination of the base to enoates **159**, giving salt **164** as an intermediate, which underwent a conjugate addition by the nitroalkane followed by elimination of DABCO, leading to product



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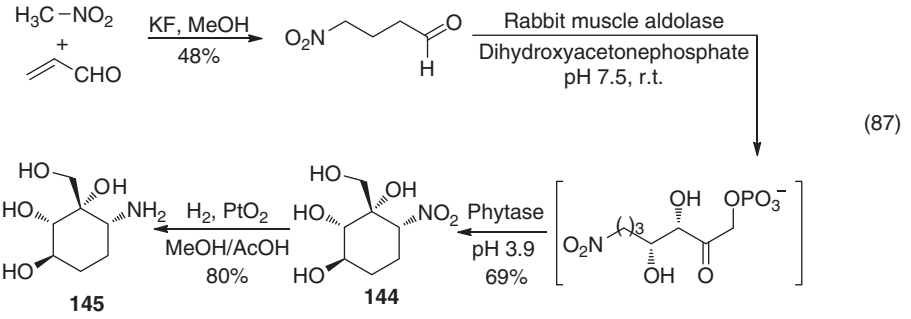

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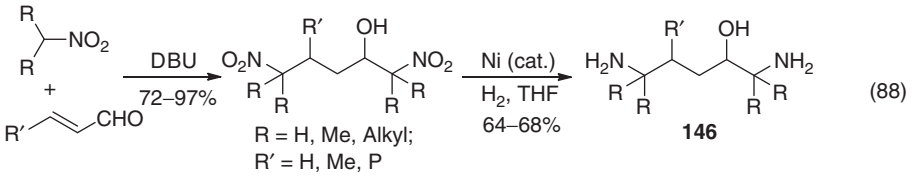


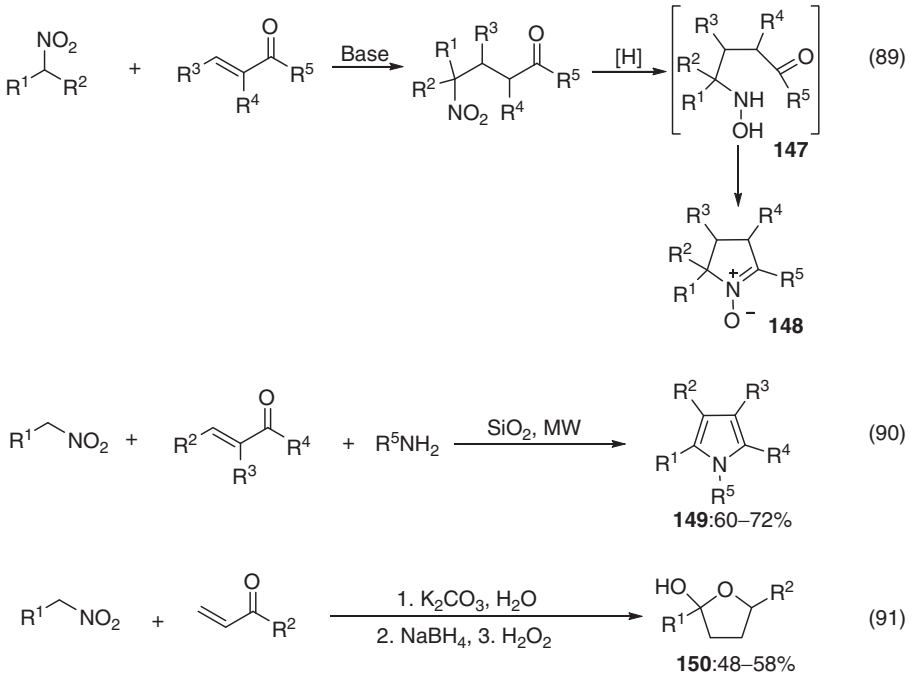
(88)

Scheme 36

165 (equation 97 in Scheme 40).[50a] Enoates **166** bringing at least one halogen atom at C-2 of the aromatic ring reacted with nitroalkanes in a tandem sequence that initially proceeded through a conjugate addition/elimination to give compound **167** (equation 98 in Scheme 40).[50b] Subsequent intramolecular aromatic nucleophilic substitution of nitro compound **167** gave rise to the formation of bicyclic derivative **168**, which quickly lost nitrous acid to afford functionalized naphthalenes **169**.

The conjugate addition of functionalized nitrocyclopentane **170** to methyl acrylate proceeded well to afford adduct **171** in quantitative yield as a single diastereomer probably because of the stereodirecting effect of the vicinal phenyl group (equation 99 in Scheme 41).[51a,b] Reduction of the nitro group using zinc in ethanolic HCl gave spirolactam **172** without any migration of the exocyclic double bond. Subsequently, lactam **C** was transformed into racemic alkaloid cephalotaxine **173**. A similar strategy can be adopted for the preparation of aza analogs of this natural alkaloid.[51c,d]

Preparation of lactone derivatives from conjugate adducts of nitroalkanes to enoates generally involves a preliminary elimination of the nitro group to give an alkene derivative or conversion of the nitro group into a carbonyl function by a Nef reaction. The conjugate addition/elimination process provided unsaturated ketoesters **174** as central intermediates for the synthesis of various butyrolactone systems (equation 100 in Scheme 41). Reduction of the alkene and carbonyl groups in **174** allowed the preparation of α-substituted-γ-methyl-γ-lactones **175**.[51e] Alternatively, the alkene function can be retained in the lactone moiety of **176** by a chemoselective reduction of the carbonyl function using the $NaBH_4/Na_2HPO_4{\cdot}12H_2O$ system.[51f] Finally, nucleophilic attack of the carbonyl group can be selectively realized using a Grignard reagent in the presence of $CeCl_3$ with consequent formation of γ,γ-disubstituted lactones **177**.[51g] Similarly, 2-alkylidene dimethyl succinates **178** can be hydrolyzed to the parent carboxylic acids and then converted into the corresponding anhydrides **179** by reaction with acetyl chloride at reflux (equation 101 in Scheme 41).[51h,i]



Scheme 37

Radical denitration allows complete removal of the nitro group by its replacement with a hydrogen atom. The conjugate addition of nitroalkane **180** in solventless conditions using macroreticular resin Amberlyst A-21 provided the adduct **181**, which was denitrated using Bu_3SnH to diester **182** and finally hydrolyzed to give (±)-phoracantholide **183** (equation 102 in Scheme 41).[51j]

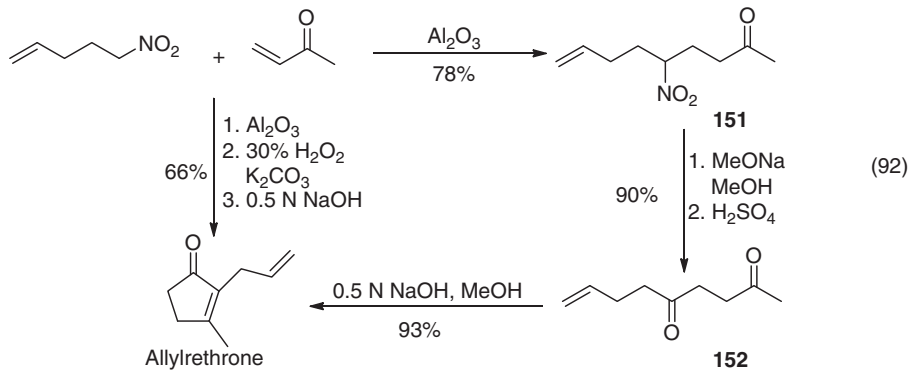
Diastereoselective conjugate addition of nitromethane to chiral (*Z*)-enoate **184** led to the synthesis of compound **185** with predominance of the *syn* stereoisomer (equation 103 in Scheme 42).[52a] Reduction of the nitro group and ring-closure affords pyrrolidinone **186**, which can be used as synthetic intermediate in the preparation of several potentially useful compounds. Nitromethane addition to diester **187** gave the adduct **188** that on reduction of the nitro group and ester hydrolysis afforded pyrrolidinone **189** (equation 104 in Scheme 42).[52b] Acid **189** can be easily transformed in a few steps into bicyclo-γ-lactam **190**, which acts as an inhibitor of penicillin-binding proteins. Nitromethane can be used not only as nucleophile but also as solvent. In the presence of KF, the tandem autoxidation/conjugate addition of nitromethane to glycoside lactone derivative occurred at room temperature to afford 2-*C*-methoxy-carbonylmethyl-2-*C*-nitromethyl-α-*D*-glycopyranoside-3-ulose **191** (equation 105 in Scheme 42).[52c]

The double- and triple-conjugate addition of nitroalkanes to electron-deficient enoates was also applied for the preparation of quaternary nitro derivatives in the presence of Triton B. By thermolysis heating elimination of nitrous acid the products **192** can be obtained (equation 106 in Scheme 43),[53a–c] whereas the quantitative reduction of the nitro group was carried out under 60 psi of hydrogen in EtOH for the synthesis of Dendron **192** (equation 107 in Scheme 43).[53d]

Piperidones are attractive synthetic targets due to their interesting pharmacological properties. Conjugate addition of β-amino-substituted nitroalkanes to enoates and subsequent cyclization of the corresponding amines can be used for the construction of such heterocyclic compounds **194** (equation 108 in Scheme 44).[54,8a,b] Chiral piperidinone **195** reacted with nitromethane to give the adduct with modest *syn* diastereoselectivity. Conversely, the conjugate addition of secondary nitroalkanes to piperidinone furnished exclusively the *anti* diastereomer (equation 109 in Scheme 44).[54c] Alternatively, nitroalkanes added to α,β-unsaturated δ-thiolactams leading to substituted piperidine-2-thiones **196**, which were easily converted into piperidones **197** in high yield (equation 110 in Scheme 44).[54d]

N-Substituted maleimides are important electron-deficient heterocyclic systems. Ballini and coworkers demonstrated that nitroalkanes reacted with maleimides in the presence of DBU to afford the corresponding adducts, which suffered elimination of nitrous acid by the excess of the base employed giving the unsaturated derivatives **198** (equation 111 in Scheme 45).[55a,b] In the conjugate addition of bromonitromethane with *N*-substituted maleimides the intramolecular nucleophilic substitution of the intermediate anion **199** was strongly favored over elimination of nitrous acid and ultimately led to the synthesis of *exo*-nitro-cyclopropanes **200** as a single diastereomer (equation 112 in Scheme 45).[55c]

The conjugate addition of nitromethane to unsaturated nitrile **201** gave the corresponding adduct **202**, which followed by catalytic hydrogenation with 10% Pd/C in MeOH/AcOH (9:1) and acylation to furnish *N*-trifluoroacetylpyrrolidine **203** (equation 113 in Scheme 46).[56a] In this process, the primary amine formed by reduction of the nitro group could react with the intermediate imine formed by reduction of the nitrile to give the intermediate pyrrolidine. Compound **203** is an intermediate for the preparation of synthetic analogs of sinefungin, a nucleoside active against viruses, fungi, and parasites. Double addition of



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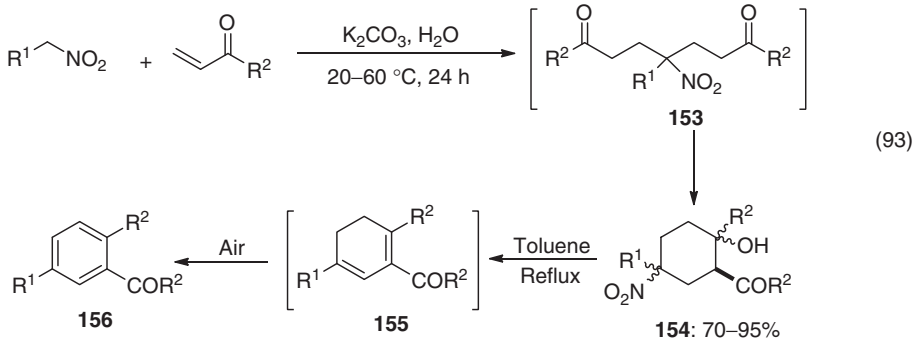

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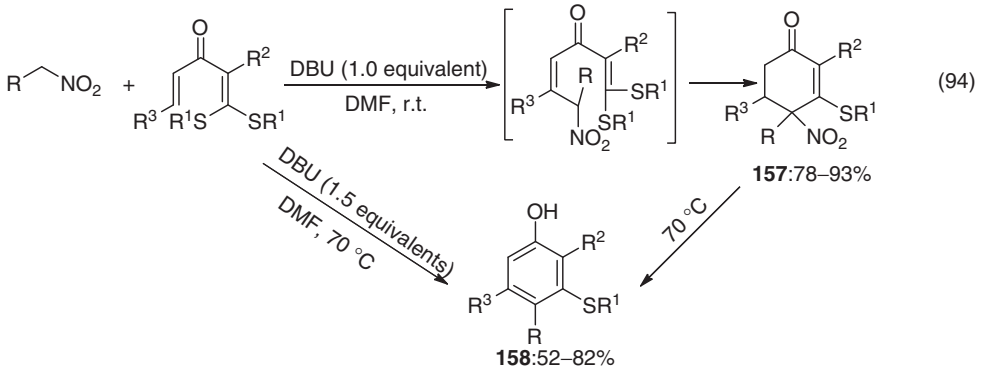


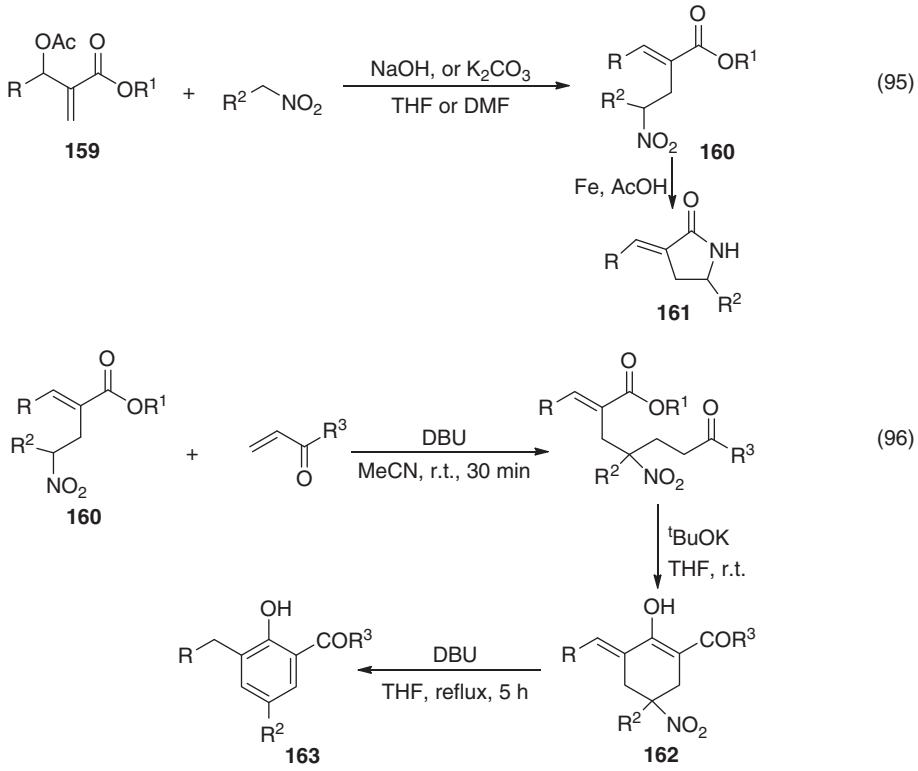
(94)

Scheme 38

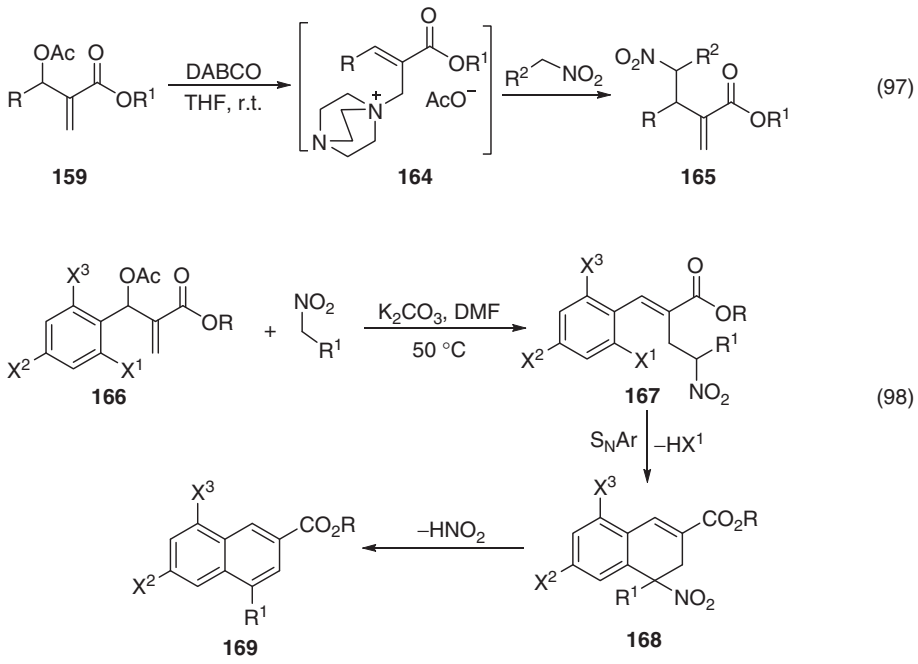
nitromethane to arylidene cyanoacetate **204** afforded the adduct **205**, which underwent an intramolecular nucleophilic addition to give cyclic derivative **206** (equation 114 in Scheme 46).[56b,c] A catalytic amount of piperidine was used, and tautomerization of imino derivative **206** occurred to give the product **208** as the main product, whereas the utilization of one equivalent of the basic promoter caused a decarboxylation of the intermediate **206**, producing cyclohexene derivative **207** as the final product.

An interesting approach to the preparation of conjugated dienones involved a conjugate addition of nitroalkanes to 2-phenylsulfonyl-1,3-dienes **209** to give nitro sulfones **210**. Conversion of the nitro group into a ketone **211** was followed by a base-induced elimination of benzenesulfinic acid leading to dienone **212** with high diastereoselectivity (>95% *ee*) (equation 115 in Scheme 47).[57a] In the presence of DBU, 2-chloro-3-phenylsulfonylpropanenitrile **213** generated *in situ* electron-deficient alkene, which reacted regioselectively with nitroalkanes at −10 °C to afford, via the usual conjugate addition/elimination mechanism, the corresponding conjugated nitriles **214** (equation 116 in Scheme 47).[57b] The double-bond configuration in most of the examples reported is *E*, but depending on the nature of the nitroalkane used, a certain amount of *Z* stereoisomer can sometimes be formed.

Conjugated nitrosoalkenes **215** are typical electron-deficient olefins that can be generated *in situ* by reaction of fluoride ions with *N*,*N*-bis(silyloxy)enamines at low temperature (equation 117 in Scheme 48).[58a] A conjugate reaction of nitronate anions, formed from the corresponding nitroalkanes, to nitrosoalkenes occurred to afford α-nitro oximes **216**. Accordingly, 1,3-dinitroalkanes **217** can be prepared by heating at reflux an aldehyde with an excess of nitromethane in the presence of basic alumina (equation 118 in Scheme 48).[58b] This tandem process involved a preliminary nitroaldol condensation and a subsequent



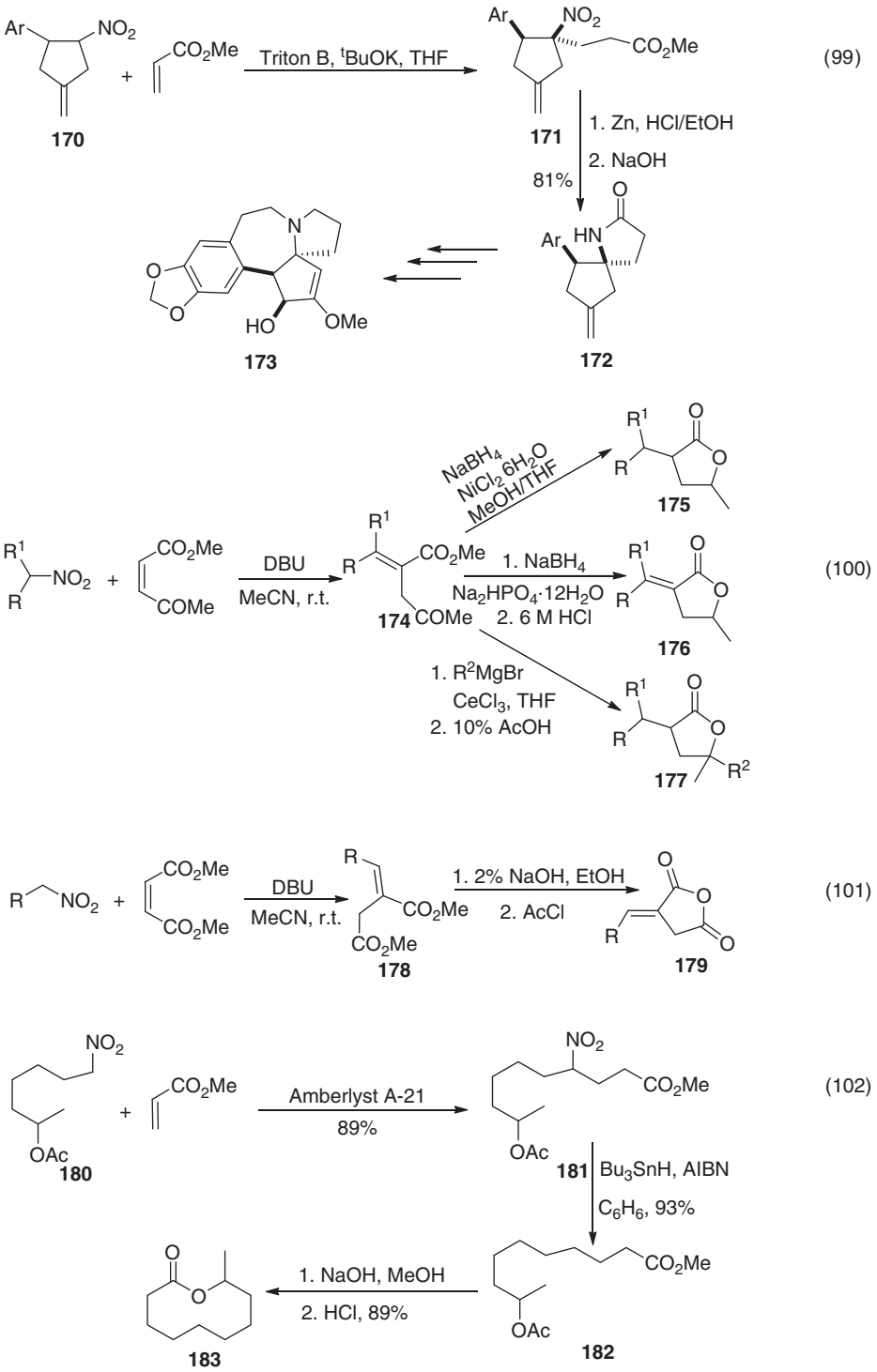
Scheme 39



Scheme 40

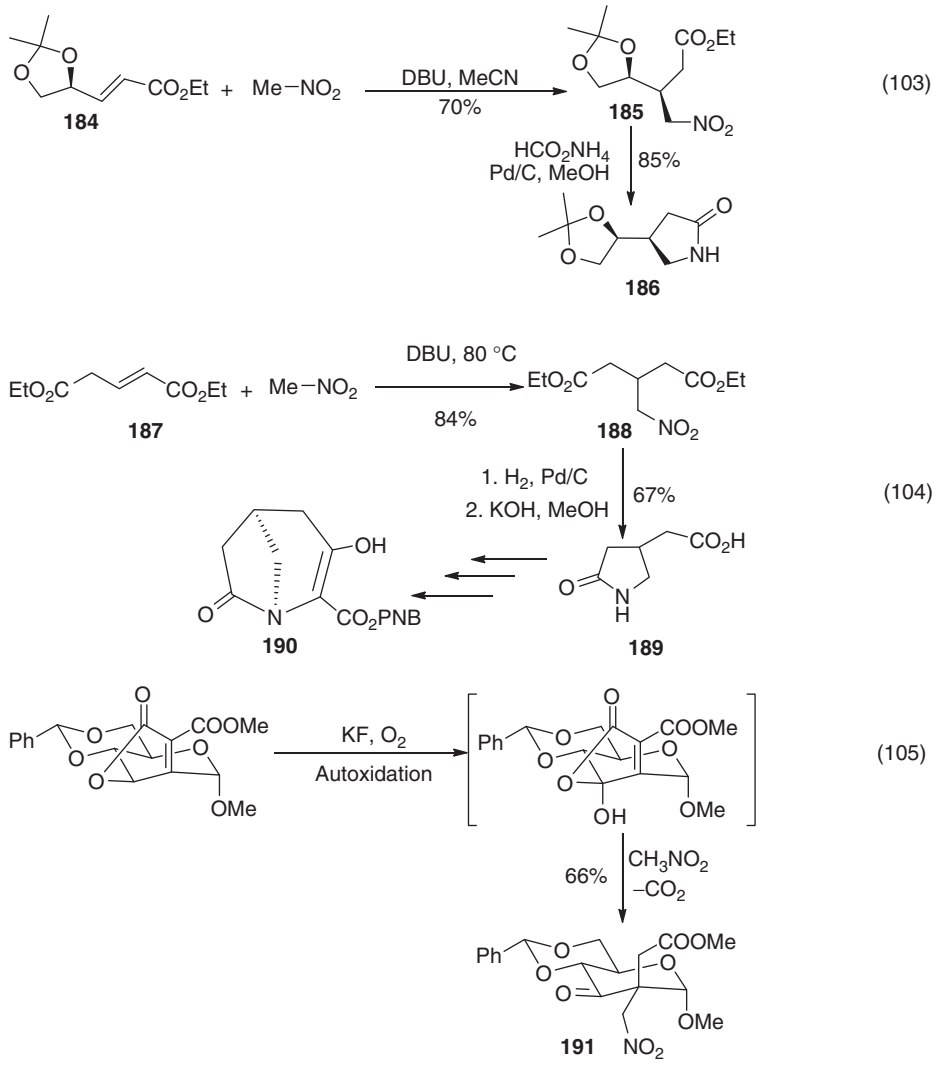
dehydration to give the corresponding nitroalkenes **218**, which further underwent a conjugate addition of the nitromethyl anion to afford the final adducts **217**.

A conjugate addition of substituted allylnitro compounds to MVK proceeded to afford nitroalkenes **219** (equation 119 in Scheme 49).[59a] Despite the basic conditions, the reaction occurred without any observed migration of the double bond. In



Scheme 41

contrast, β-alkyl nitroalkenes reacted with α,β-unsaturated carbonyl compounds in the presence of secondary amines (Lewis base catalysts) to give γ-nitro-γ-vinyl carbonyl compounds **220** in 70–90% yield (equation 120 in Scheme 49).[59b] In this tandem transformation, the nucleophilic addition of the Lewis base first attacks β-alkyl nitroalkenes to form the nitrocarbanion intermediate. The nitrocarbanion addition to β-alkyl nitroalkenes is in equilibrium, and intermediate nitroalkene oligomers can dissociate and reproduce the nitrocarbanion, leading to the addition of a less reactive Michael receptor. The corresponding adducts could easily be converted into lactam, allylic alcohol, and enone derivatives in good yields. Recently, a series of fluoronitroalkanes were used as Michael donors in conjugate addition reaction. In the presence of tetramethylguanidine, the Michael adducts **221**



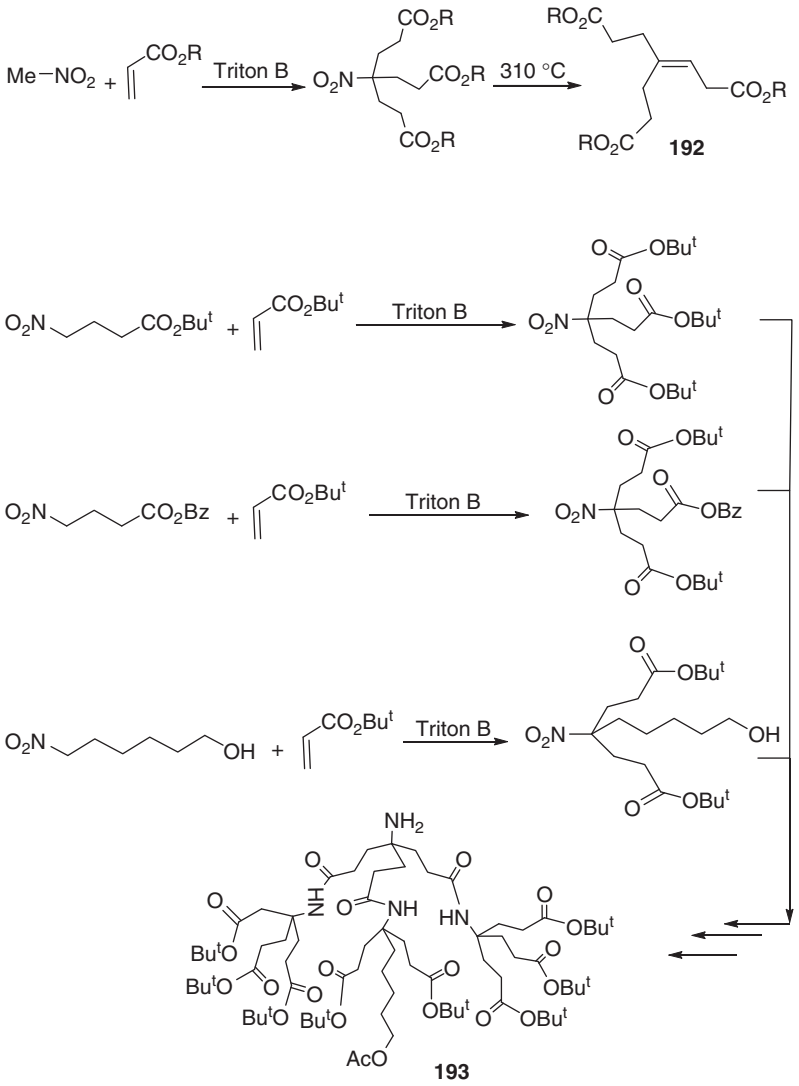
Scheme 42

with a fluorine-containing quaternary center were obtained in 45–85% yield (equation 121 in Scheme 49).[59c] This conjugate reaction provided a practical method for the preparation of biologically useful fluorinated derivatives.

4.01.2.1.1.4 Indoles and pyrroles

The Friedel–Crafts-type conjugate addition of electron-rich aromatic compounds, such as indoles and pyrroles, to electron-deficient alkenes has attracted much attention as one of the most important C–C bond-forming reactions. Due to the dramatic difference in reactivity between the 2- and 3-positions of indoles and pyrroles, the formation of 3-substituted indoles is usually achieved (equation 122 in Scheme 50),[60] whereas the addition of pyrroles fulfills the synthesis of 2-substituted derivatives (equation 123 in Scheme 50).[61] Generally, the conjugate addition of indoles and pyrroles to Michael acceptors can be catalyzed by various bases, Brønsted acids, and Lewis acids under mild conditions. Furthermore, some transition metal complexes were also used in the Friedel–Crafts-type conjugate addition reactions of indoles and pyrroles. In recent years it has been reported that these additions can proceed well under aqueous media, microwave-assisted, or free-solvent conditions.

Notably, the conjugate addition reactions of indoles have also been applied for the synthesis of some fused heterocyclic compounds. Perumal and coworkers described a $KHSO_4$-catalyzed addition of indoles to *β*-nitrostyrenes **222** possessing *O*-propargyloxy groups to generate nitroalkanes **223**. In the presence of $(Boc)_2O$ and *N*,*N*-dimethylaminopyridine (DMAP), the adducts underwent a sequential intramolecular cycloaddition of nitrile oxide with alkyne to form isoxazolobenzoxepanes **224** (equation 124 in Scheme 51).[62a] Furoindolines with a quaternary carbon center at the C-3 position represent structural moieties existing widely in natural products. You and coworkers developed a Lewis acid-catalyzed cascade dearomatization of *N*-substituted tryptophols **225** including conjugate addition and subsequent iminium ion trapping to construct the furoindoline framework **226**



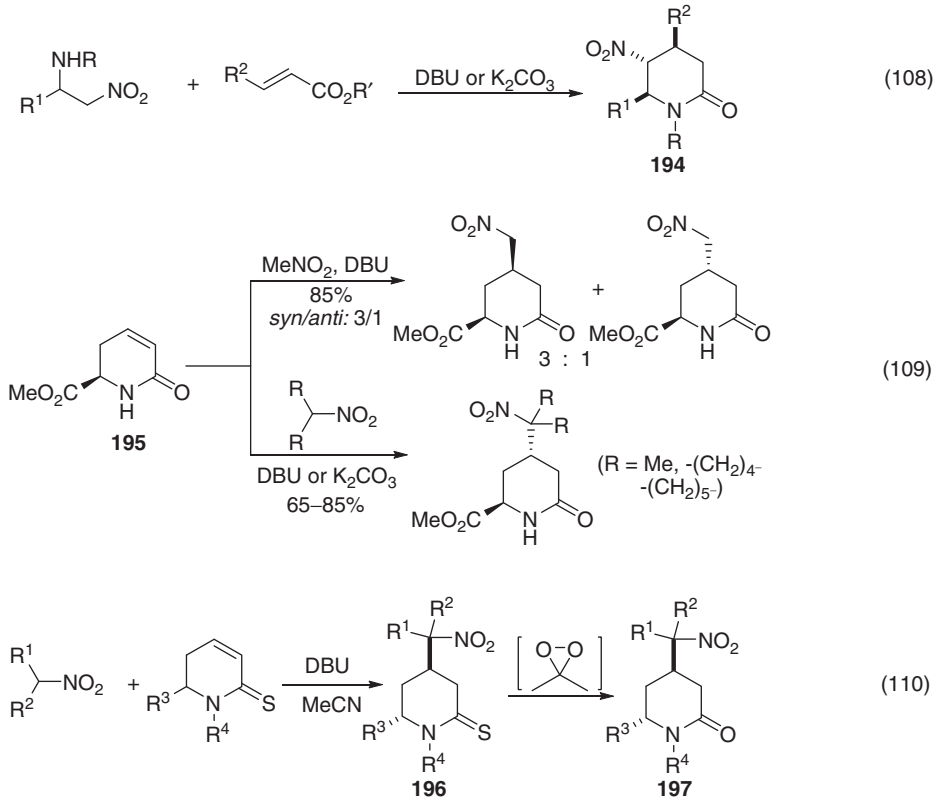
Scheme 43

(equation 125 in Scheme 51).[62b] Further transformation of the cascade products furnished the corresponding furoindoline derivatives.

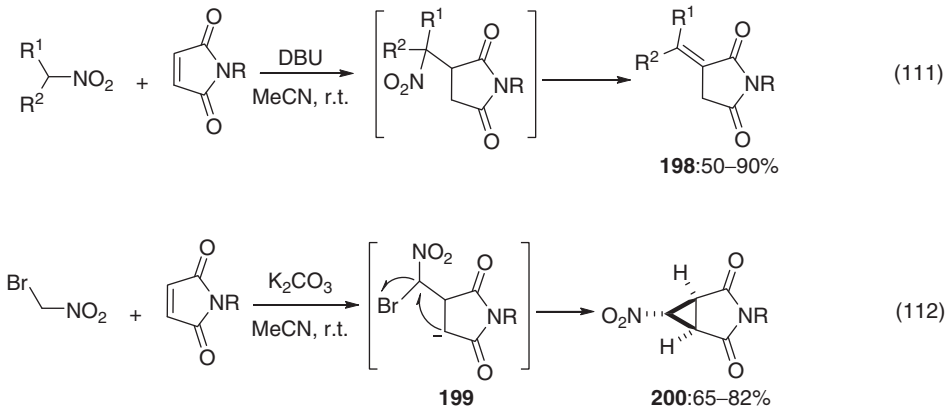
Oxindoles can also act as good carbon nucleophilic reactants. Zhou and coworkers described a quinidine-catalyzed Michael addition of unprotected 3-substituted oxindoles **227** with nitroolefins to give the conjugate adducts **228** with two adjacent quaternary–tertiary carbon centers (equation 126 in Scheme 52).[63a] Subsequent investigation revealed that alkaloid-based chiral thiourea catalysts promoted this conjugate addition, affording the adducts in up to 85% *ee* with moderate diastereoselectivity. A series of spirocyclopentaneoxindoles **230** with four contiguous stereocenters were constructed by using 4-(*N*-protected oxindol-3-yl)but-2-enates **229** and *β*-nitrostyrenes. The reaction proceeded through tandem inter- and intramolecular double-Michael addition with high diastereoselectivity (16:1–30:1 *dr*). In the presence of $NaBH_4/NiCl_2{\cdot}6H_2O$, the adducts could be further transformed into tetracyclic molecules **231** (equation 127 in Scheme 52).[63b]

4.01.2.1.1.5 Stabilized ylides

Stabilized ylides have also been used as potential nucleophilic donors in many conjugate addition reactions. The obtained adducts still retain the zwitterionic moiety, and therefore further intramolecular transformations very often follow the main addition process. Treatment of the nitrone dipole **232** with a tertiary amine in the presence of lithium salts followed by addition to electron-deficient alkenes furnished *N*-hydroxypyrrolidines **233** via a stepwise conjugate addition/intramolecular Mannich-type process (equation 128 in Scheme 53).[64] Accordingly, nitrone dipole was converted into a nitrone ylide so that it underwent a nucleophilic addition reaction rather than the expected 1,3-dipolar cycloaddition. Although the nitrone oxygen atom does not participate directly in the formation of the dipole, it plays a crucial role in the reaction by promoting the formation of a chelate responsible for the stereochemical course of the reaction.



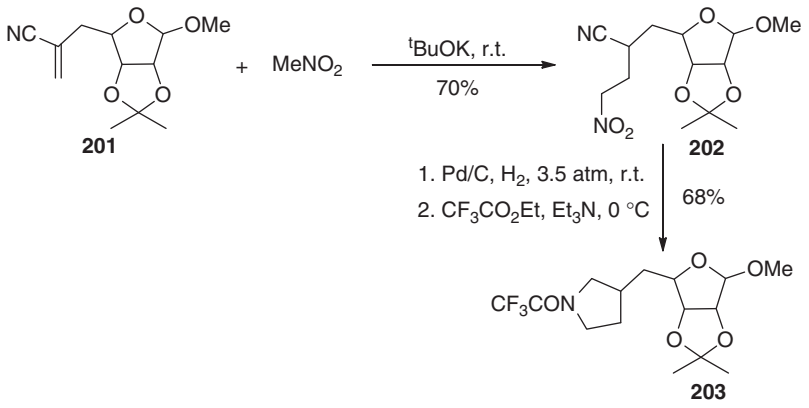
Scheme 44



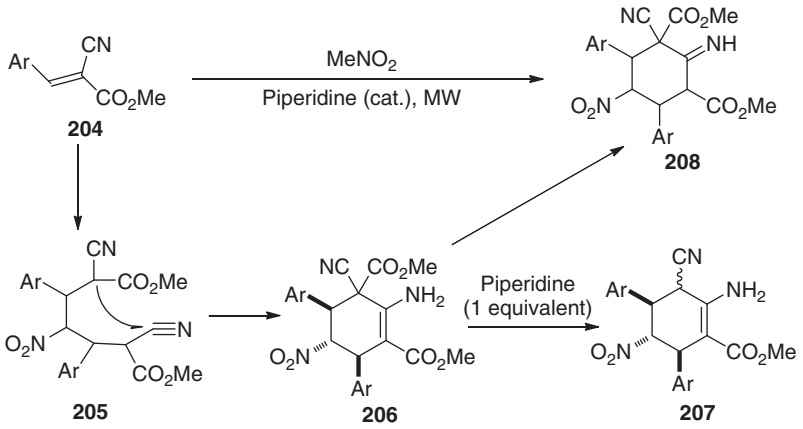
Scheme 45

In the presence of Cs_2CO_3, cinchona-derived ammonium salts **234** also reacted smoothly with 3-aryl-subsituted 2-nitro acrylates, affording (*R*,*R*)-isoxazoline *N*-oxides **235** as single diastereomers (*trans*/*cis* > 99/1) with over 96% *ee* in good yields (equation 129 in Scheme 53).[65a] The enantiomeric excesses were nearly independent of the substituents of the aryl and heteroaryl groups. Based on this research work, Gunasekaran et al. described a triethylamine-promoted tandem reaction of 2-(3-indolylcarbonyl)-3-aryl-2-propenenitriles **236** with (2-aryl-2-oxoethyl)pyridinium bromides **237**. *trans*-5-Aroyl-2-(indol-3-yl)-4-aryl-4,5-dihydrofuran-3-carbonitriles **238** were obtained in excellent yield and diastereoselectivity (equation 130 in Scheme 53).[65b]

Under basic conditions, sulfonium, telluronium, and arsonium allylides could easily generate *in situ* the corresponding ylides, which reacted with α,β-unsaturated carbonyl compounds to give polysubstituted cyclopropanes **239** (equation 131 in Scheme 54).[66] As a well-accepted mechanism, the Michael addition of ylide to electron-deficient alkenes produces a betaine intermediate. This intermediate can potentially undergo intramolecular C-substitution, which leads to the formation of cyclopropanes.

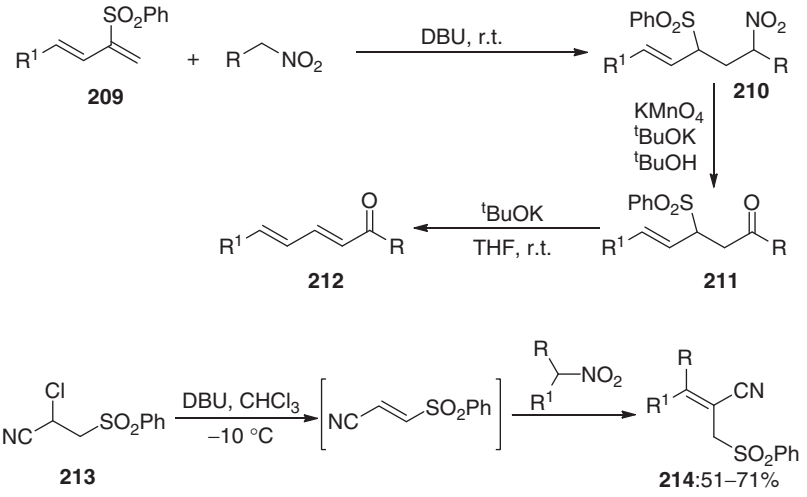


(113)



(114)

Scheme 46

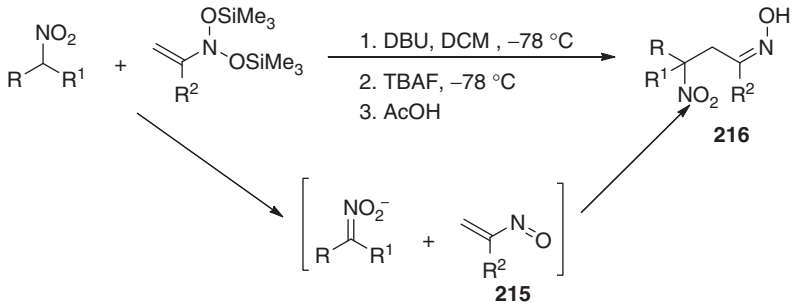


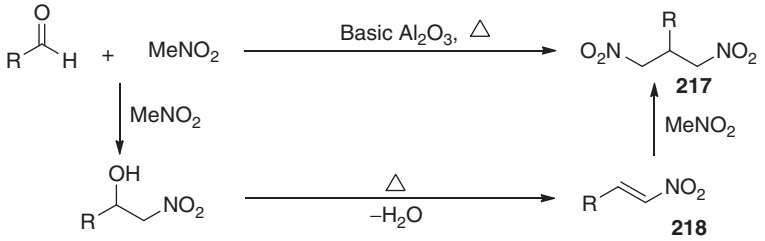
(115)

(116)

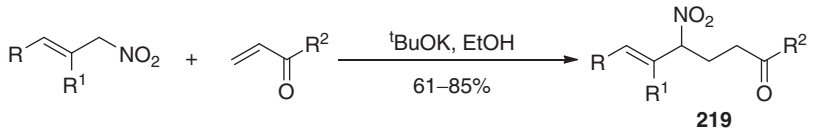
Scheme 47

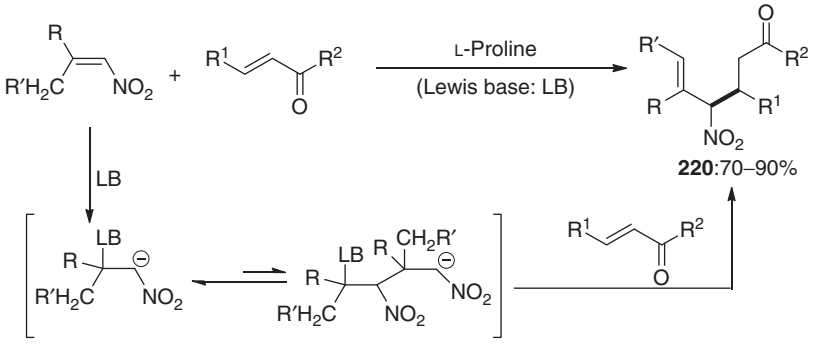
In contrast, the conjugate addition of sulfur ylides **240** to α-nitro-α,β-unsaturated esters **241** delivered the addition intermediates, which underwent intramolecular substitution to give isoxazoline *N*-oxides (equation 132 in Scheme 35).[67] The diastereomeric ratio (*trans*/*cis*) was up to 99/1, and no cyclopropane derivatives were observed.[67c] Camphor-derived sulfonium salt for the enantioselective synthesis of isoxazoline *N*-oxides proved to be inefficient, and only low *ee* values (<40%) were obtained. Similarly, dialkylsulfonium salts **240** reacted with α,β-unsaturated ketones in the presence of Cs_2CO_3, leading to the formation of dihydrofuran derivatives **242** with high selectivities rather than cyclopropanes, probably because the steric hindrance of α-substituents of the carbonyl group retarded the 1,3-substitution to generate cyclopropanes (equation 133 in Scheme 55).[67d]

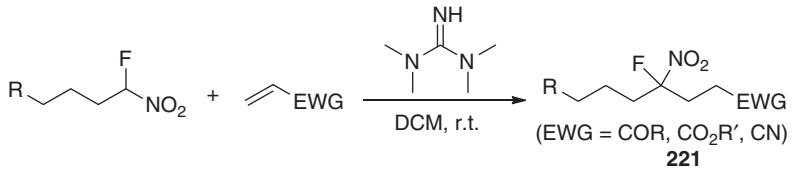




Scheme 48

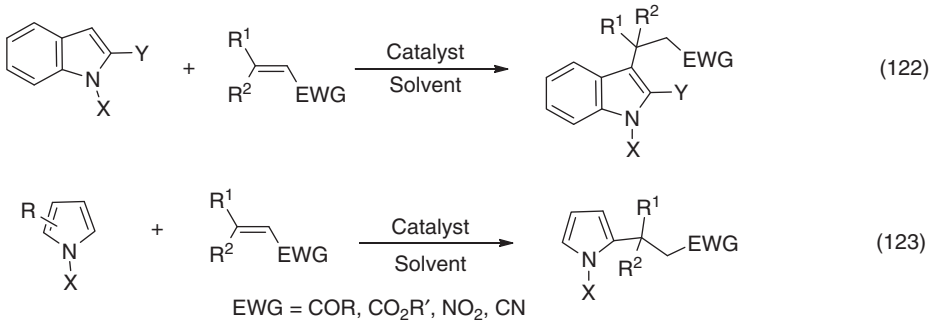




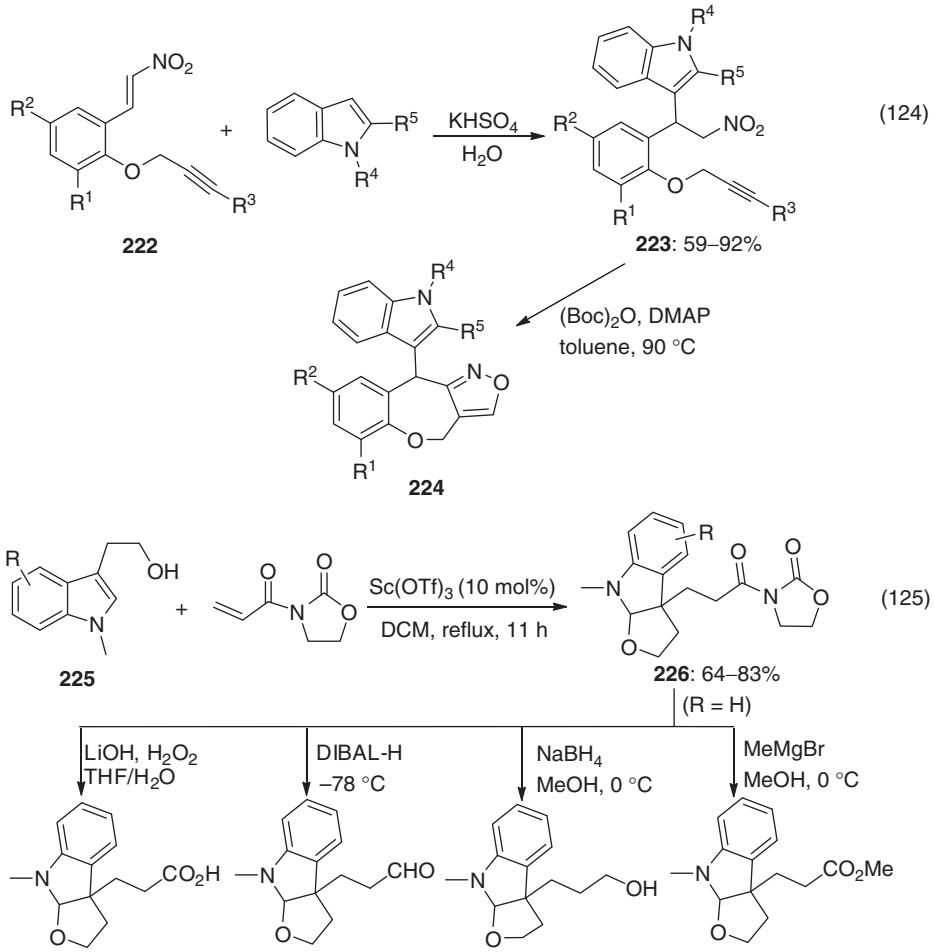


Scheme 49

Sulfur ylide **244**, generated *in situ* from the corresponding sulfonium salt **243** under basic conditions, underwent an intermolecular conjugate addition with *α,β*-unsaturated ketones to form the addition intermediate. Subsequent proton transfer and intramolecular ylide epoxidation afforded the cyclohexadiene epoxide derivatives **245** (equation 134 in Scheme 55).[67e] When the conjugated eyn-enones **246** were employed as electron-deficient acceptors, the sulfonium salt **243** delivered a series of novel bicycle[3.1.0]hex-2-enes **247** in 30–85% yields. This reaction involved a tandem conjugate addition/ylide annulation process. It is interesting that the stereochemistry of all three newly formed carbon stereogenic centers and the double bond could be controlled in this domino process (equation 135 in Scheme 55).[67f]

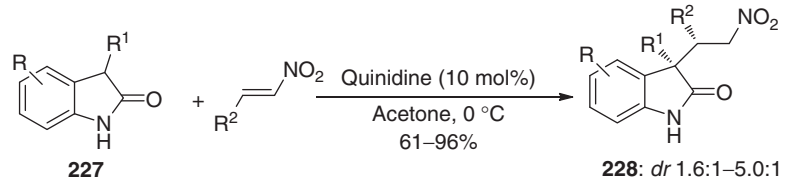


Scheme 50

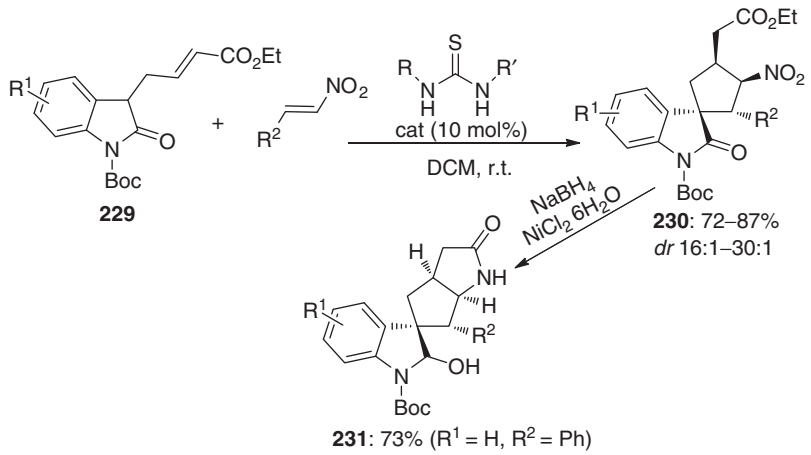


Scheme 51

The phosphorus ylide-initiated conjugate addition reaction has also been established as a promising method for the preparation of the highly functionalized compounds. Over half a century ago, the Alkonyi and Wuest groups developed a reaction of substituted allylbromide Wittig salt with alkylidene *β*-ketoesters **248** for the synthesis of substituted cyclohexadienes **249** (equation 136 in Scheme 56).[68a,b] In the presence of *n*-BuLi, the generated allyl anion underwent conjugate addition to alkylidene *β*-ketoester to give the intermediate, which further rearranged through 1,5-sigmatropic shift to afford the phosphonium betaine. Proton transfer to the ylide followed by intramolecular Wittig condensation could afford the substituted cyclohexadienes. The results of variable temperature NMR spectroscopy and X-ray crystallography indicated that the added ylide intermediate could undergo rapid conformational interconversion.[68e] The potential application of this tandem conjugate addition/Wittig reaction has further been demonstrated as a key step in the synthesis of the 9-*cis*-tetinoic acid **250**[68c] and taxol A-ring **251**.[68d] Furthermore, the



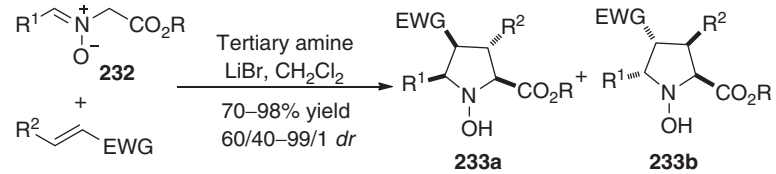
227 228: *dr* 1.6:1–5.0:1 (126)



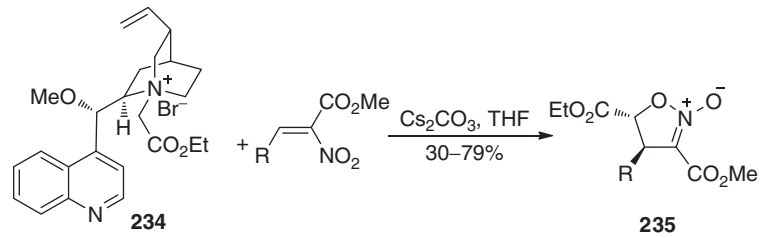
229 230: 72–87%, *dr* 16:1–30:1 (127)

231: 73% (R^1 = H, R^2 = Ph)

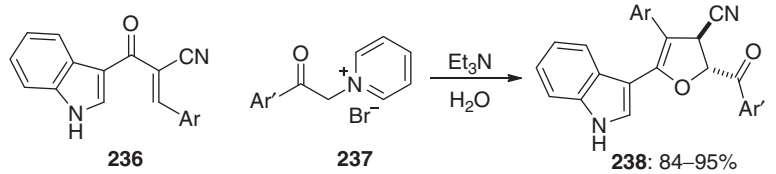
Scheme 52



232 233a 233b (128)



234 235 (129)

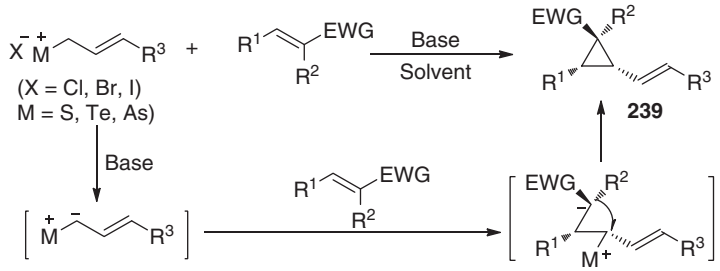


236 237 238: 84–95% (130)

Scheme 53

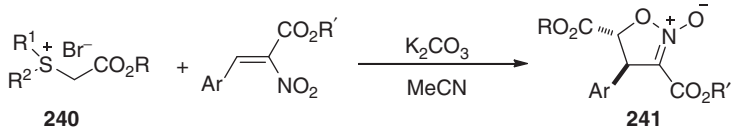
reaction of a crotonate-derived chiral phosphonium salt with α,β-unsaturated carbonyl compounds in the presence of Cs_2CO_3 provided optically active 1,3-cyclohexadiene derivatives **252** with up to 90% *ee*.[68f]

When carbonyl-stabilized ylides were treated with α,β-unsaturated carbonyl compounds, the corresponding dicarbonyl ylides were formed as stable solids (equation 137 in Scheme 56). Subsequent oxidation of the added ylides with O_2 provided tricarbonyl products **253**,[69a] whereas Ph_3PO-elimination between the ylide function and the δ-carbonyl group led to the formation of the dienes **254**.[69b] By treating BH acetates with palladium acetate and the stabilized ylide (ethoxycarbonylmethylene)

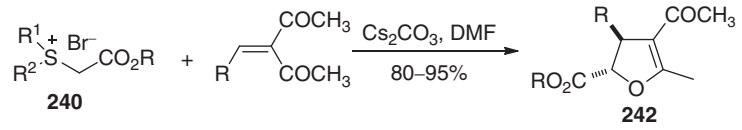


(131)

Scheme 54



(132)



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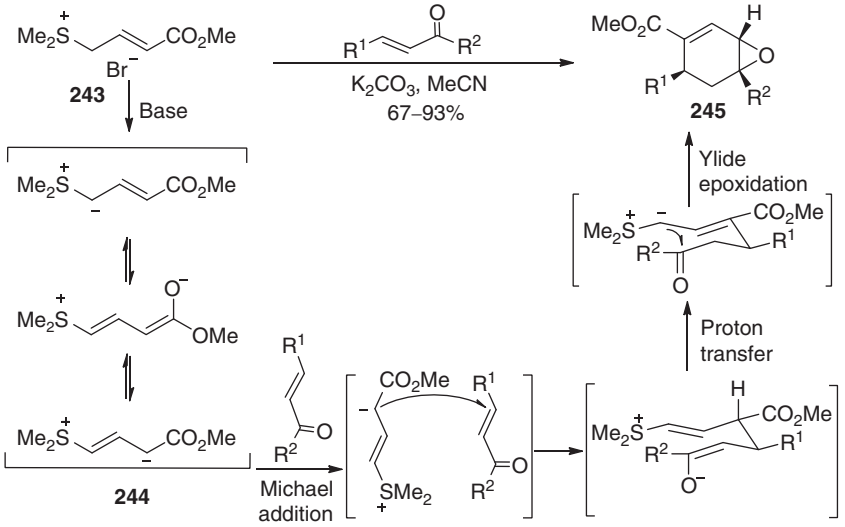

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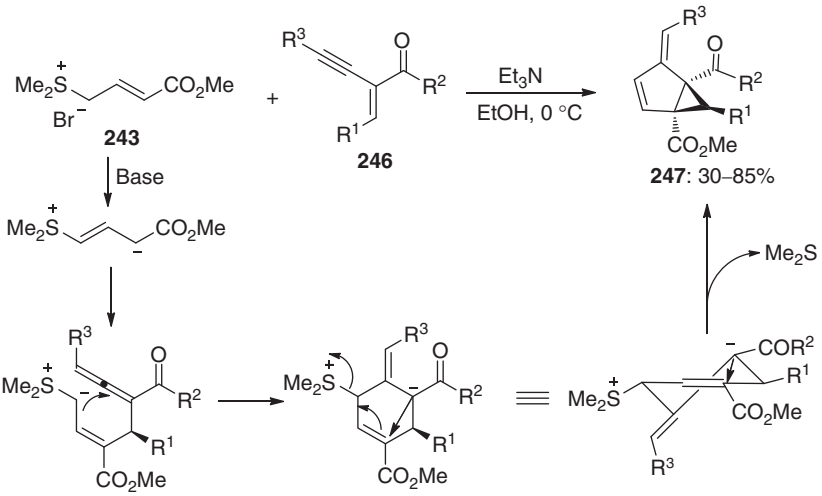
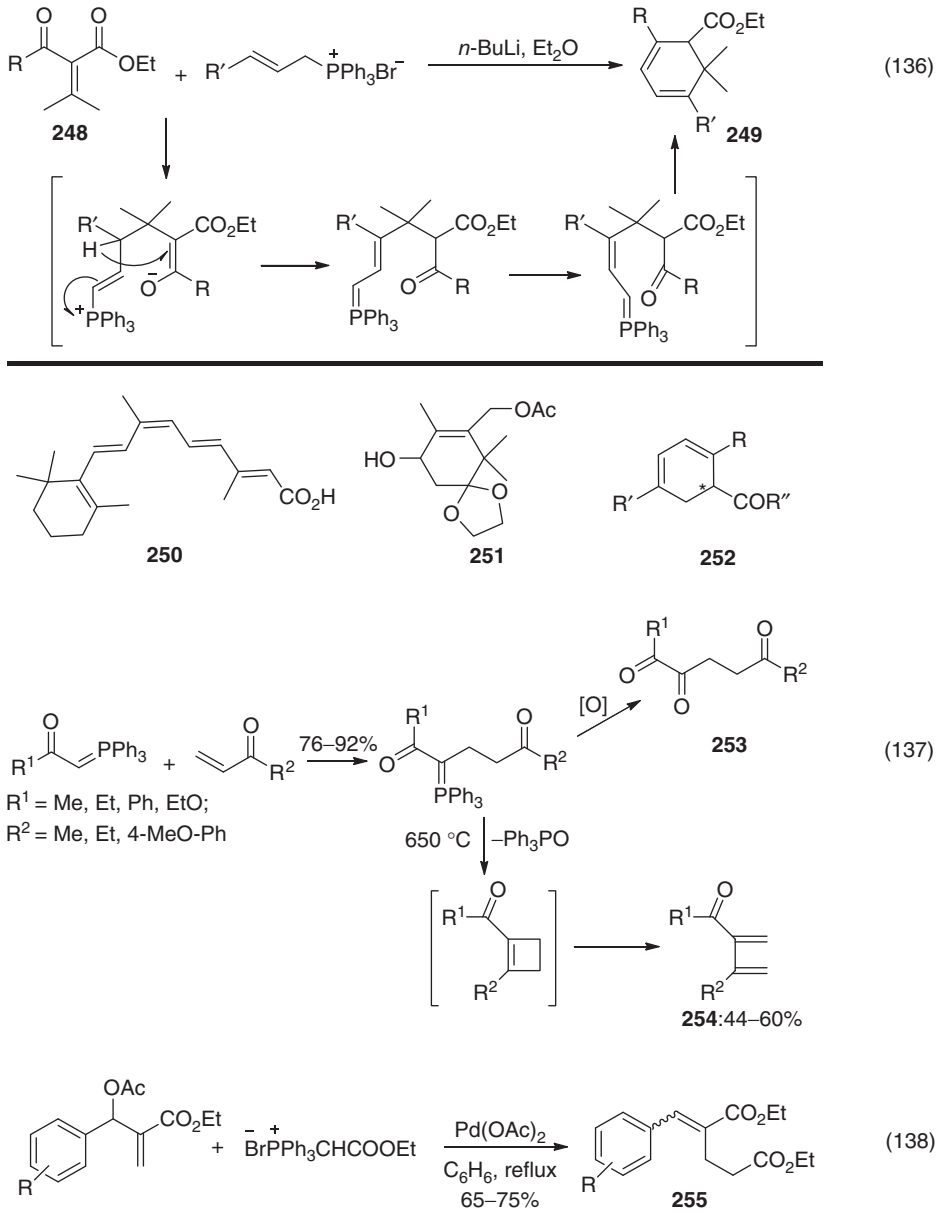


(135)

Scheme 55

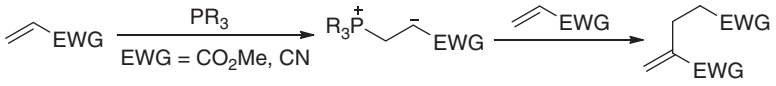


Scheme 56

triphenylphosphorane, a series of *Z*- and *E*-isomers of trisubstituted alkenes **255** were obtained via the one-pot conjugate addition process (equation 138 in Scheme 56).[69c]

Methenyl-containing zwitterionic species, generated *in situ* from electron-deficient alkenes and allenes in the presence of nucleophilic catalysts (such as tertiary phosphines and amines), also react with the second electron-deficient alkenes via homo- and heterodimerization to give the conjugate adducts.[70] In 1963, Rauhut and Currier developed the first phosphine-catalyzed dimerization of electron-deficient alkenes, acrylonitrile, and ethyl acrylate, in what has become known as the RC reaction (equation 139 in Scheme 57).[70b] More than 20 years later, three groups reported amine-catalyzed variants of the RC transformation (equation 140 in Scheme 57).[70c–e] Based on these pioneering studies, a number of zwitterion-mediated conjugate reactions have been developed for the facile construction of carbon–carbon bond in organic synthesis. In 1995, Zhang and Lu found that the treatment of ethyl α-allenoate **256** with Ph_3P results in the generation of a zwitterionic enolate-like intermediate as 1,3-dipole, which reacted with electron-deficient alkenes to give the cycloadducts **257** (equation 141 in Scheme 57).[71] Although the reaction process involved a conjugate addition,[71e] cycloadditions of allenoate-PR_3 are beyond the scope of this chapter.

Hwu et al. presented a related method for the α-alkylation of α,β-unsaturated enones using DBU as nucleophilic amine and 1,3-dimethyl-2-imidazolidinone (DMI) as solvent. Michael acceptors ethyl acrylate, acrylonitrile, and phenyl vinyl sulfone were employed in the RC reaction with 2-cyclohexen-1-one and 3-penten-2-one, providing the corresponding α-substituted enones



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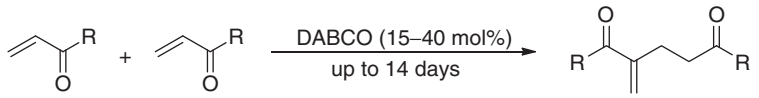

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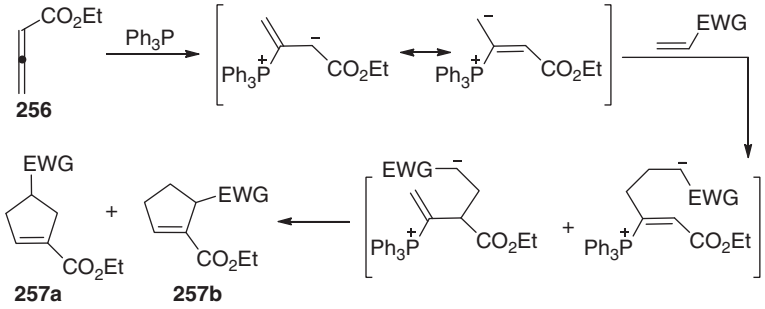
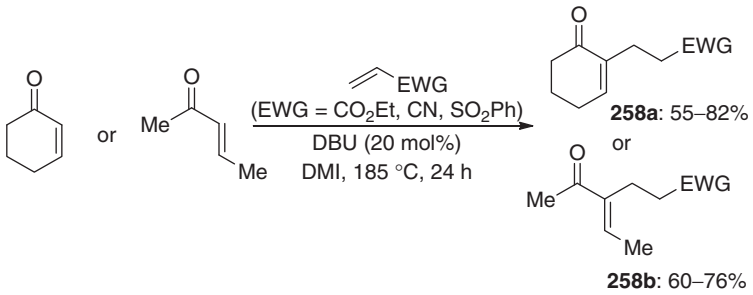


(141)

Scheme 57

258a and **258b** in 55–82% yields (equation 142 in Scheme 58).[72a] However, in the absence of alternative Michael acceptors, the dimerization of 2-cyclohexen-1-one was also possible, providing the corresponding product **259** in 85% yield under identical conditions. The control experiments indicated that 2-cyclohexen-1-one, possessing acidic γ-protons, could undergo deprotonation by DBU (vs. nucleophilic conjugate addition) to provide dienolate intermediate. Subsequent Michael addition with the desired activated alkene, followed by olefin migration, provided the observed α,β-unsaturated enones **259** (equation 143 in Scheme 58). However, the dimerization of sluggish β-substituted Michael acceptors under phosphine-based catalysis was also achieved at ambient or elevated pressure (equation 144 in Scheme 58).[72b–e]



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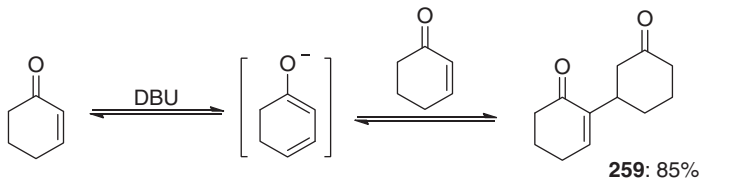

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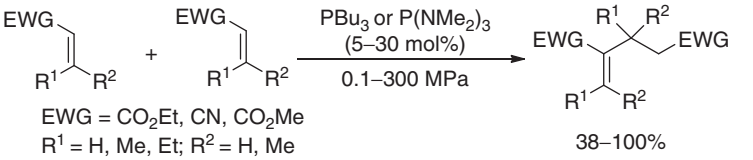
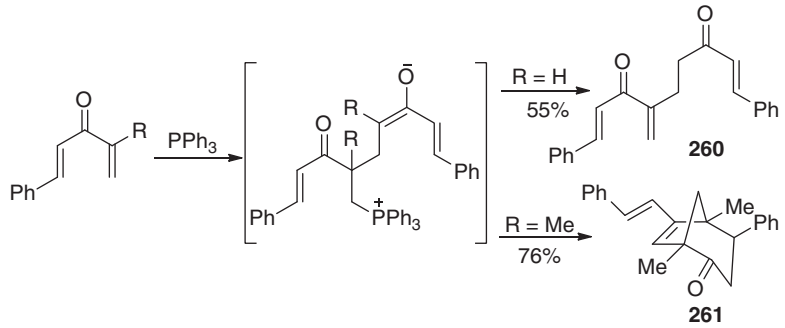


(144)

Scheme 58

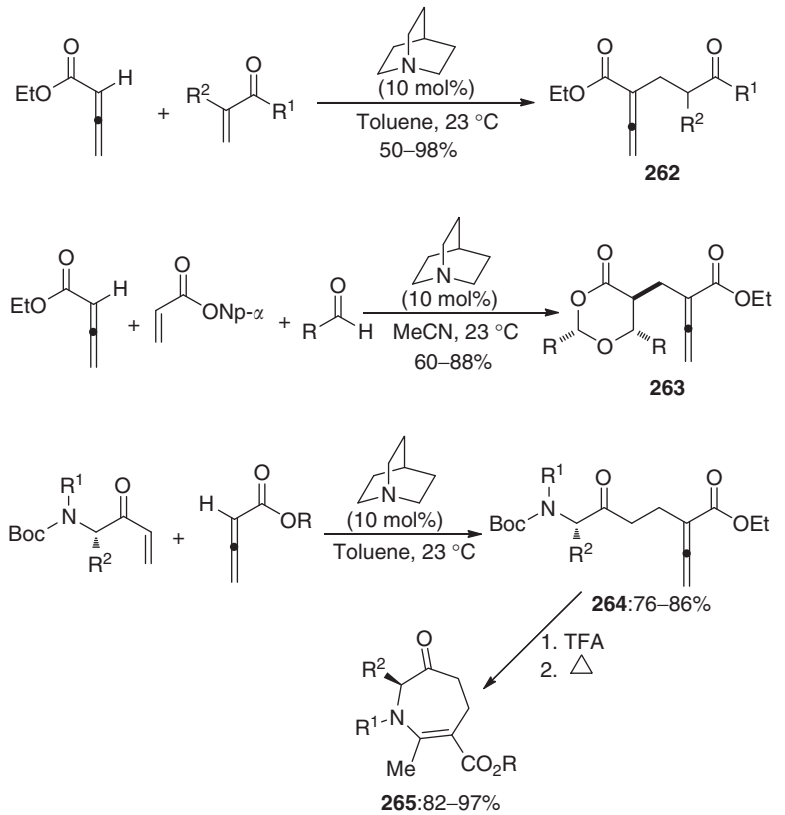
In the case of divinyl ketones, McDougal and Schaus have demonstrated divergent reactivity with different substituted substrates to produce either traditional RC products or bicyclo[3.2.1]octenones with two bridgehead quaternary carbon centers (equation 145 in Scheme 59).[73] When 1,4-diene-3-one was employed in the cyclization reaction in the presence of PPh_3 (100 mol%), facile α-deprotonation of intermediate afforded RC product **260** in 53% yield. Alternatively, in the absence of the requisite α-proton, the generated enolate underwent intramolecular Michael addition and *in situ* intramolecular Wittig olefination with the α,β-unsaturated ketone to generate bicycle **261** in good yield (76%).



(145)

Scheme 59

Evans and Miller found that the quinuclidine-catalyzed reaction of various α,β-unsaturated carbonyl compounds with allenoates underwent a traditional RC pathway, providing α,α'-disubstituted allenoates **262** in good-to-excellent yields (equation 146 in Scheme 60).[74a] Furthermore, a three-component coupling reaction of allenoate, acrylate, and aldehydes also proceeded to afford tandem products **263** with 60–88% yields (equation 147 in Scheme 60). This methodology was expanded to include the coupling of α-amino acid-derived vinyl ketones with allenic esters to provide a series of allenoate derivatives **264**, which were then elaborated to give synthetically useful chiral azacycles **265** through a trifluoroethanoic acid (TFA) deprotection/7-*endo-dig* cyclization/isomerization reaction sequence (equation 148 in Scheme 60).[74b]



(146)

(147)

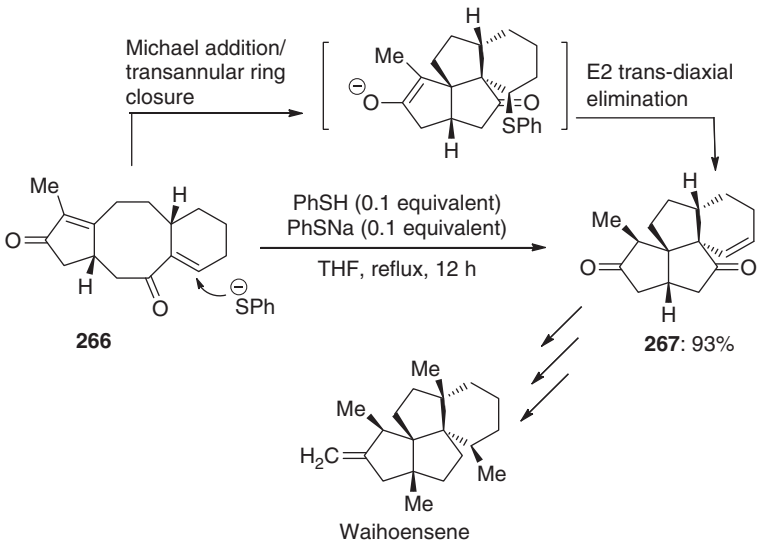
(148)

Scheme 60

4.01.2.1.2 Intramolecular additions

Intramolecular addition of carbon nucleophiles to electron-deficient alkene presents an efficient method to construct five- and six-membered rings, such as multisubstituted cyclopentane/cyclohexane, cyclopentene/cyclohexene, and (benzo)bicyclic compounds. When heteroatoms are involved in the addition, lactone, pyrrolidine/piperidine, hydrothiophene, and benzofuran/chromene derivatives can also be prepared.

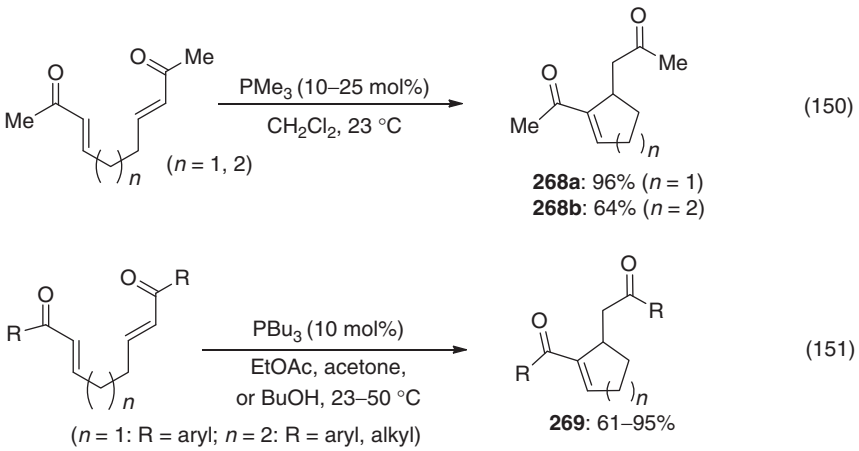
In recent years, great progress has been made in tandem reactions and domino reactions involving intramolecular Michael addition. Among these, one important reaction is the intramolecular Rauhut–Currier reaction. In 1999, Erguden and Moore reported that the cycloisomerization of tricyclic bis(enone) **266** catalyzed by thiophenol and sodium thiophenolate provided angularly fused tetraquinane **267** in excellent yield, which has the same tetracyclic ring system found in the natural product waihoensene. The cycloisomerization proceeded through a tandem sequence of reactions, including initial conjugate addition of the thiolate followed by transannular Michael reaction and an intramolecular E2 trans-diaxial elimination reaction (equation 149 in Scheme 61).[75a]



(149)

Scheme 61

In 2002, Roush and coworkers employed trimethylphosphine (equation 150 in Scheme 62) in methylene chloride at ambient temperature to provide bis(methyl) products **268**.[75b,c] In the same year, Krische and coworkers used PBu_3 in various solvents at ambient and elevated temperatures (23–50 °C) in the analogous cyclization providing a variety of cyclopentene and cyclohexene products **169** (equation 151 in Scheme 62).[75d] Both the Roush and Krische groups demonstrated that trialkylphosphines catalyze the cycloisomerization of five- and six-membered symmetrical and unsymmetrical bis(enones) with high efficiency. The relative order of reactivity of phosphine-based catalysts for the intramolecular RC reaction was empirically determined: $PMe_3 > PBu_3 >> PCy_3 >> PPh_3$.[75b–d] They also investigated the solvent effect and steric effect, as well as regioselectivity and diasteroselectivity.

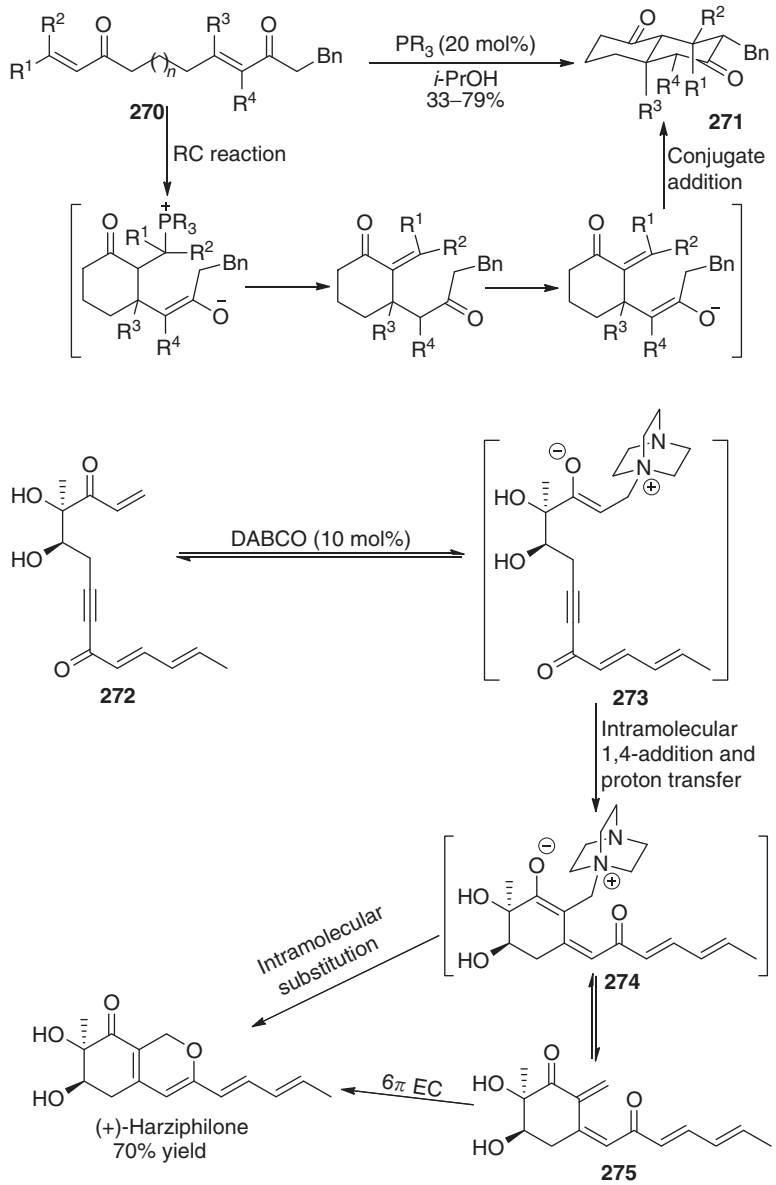


(150)

(151)

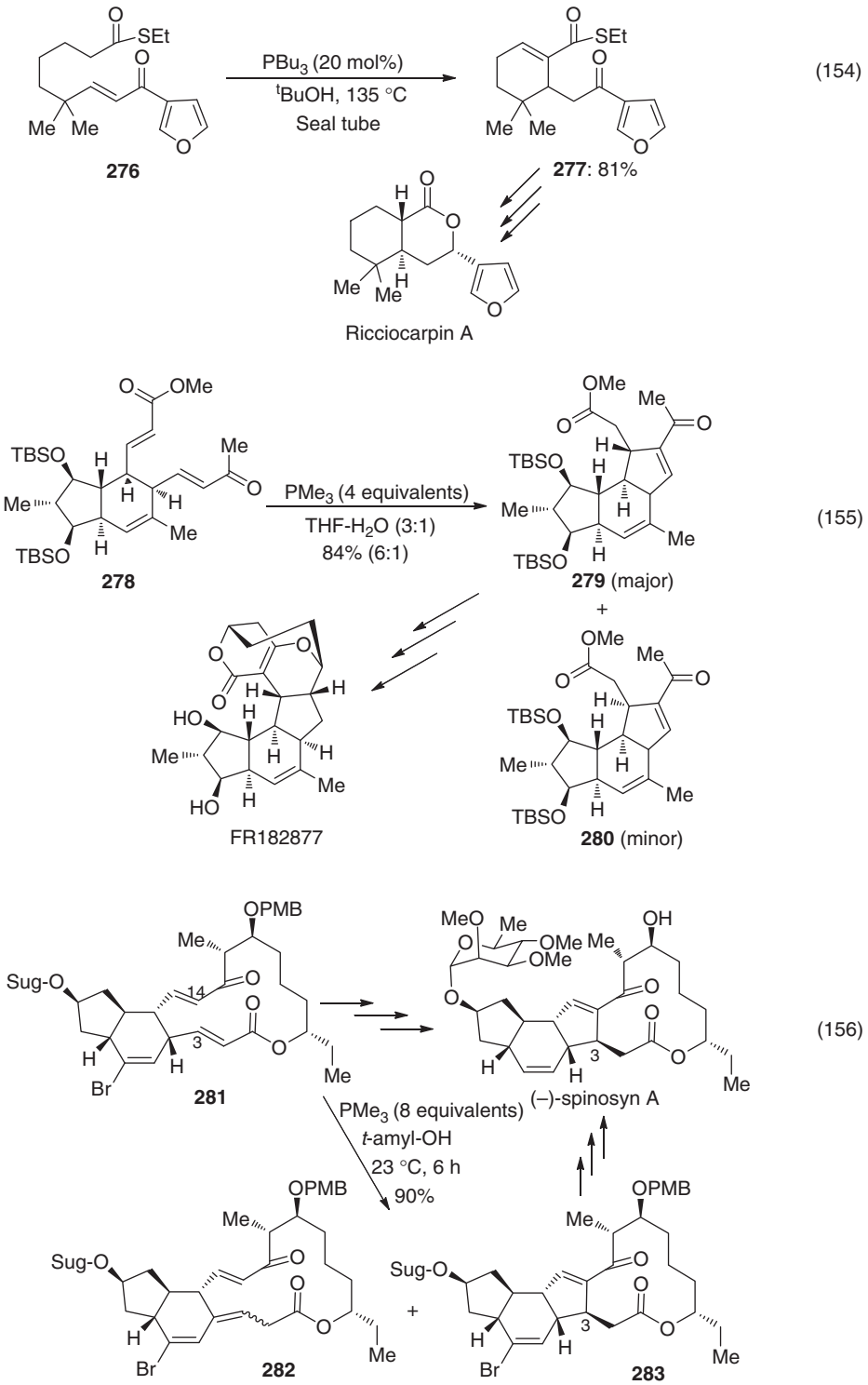
Scheme 62

The RC transformation has also been employed in the generation of bicyclic systems when followed by a subsequent transformation. Couturier et al. described a Lewis base-catalyzed cycloisomerization of bis(enones) **270** to decalins **271**.[76a] In this process, a trialkylphosphine mediates the Rauhut–Currier reaction via nucleophilic activation of a Michael acceptor, followed by conjugate addition to a second acceptor (equation 152 in Scheme 63). Sorensen's group developed the direct conversion of an acyclic polyunsaturated diketone **272** to the HIV-1 inhibitor harziphilone in 70% yield under the catalysis of DABCO (equation 153 in Scheme 63).[76b] The addition of DABCO to enone **272** led to the formation of zwitterion **273**. An intramolecular conjugate addition and a proton transfer could then generate an alternative zwitterion **274**. A simple β-elimination reaction returned the nucleophilic catalyst to the reaction medium and afforded **275**, thus enabling a final 6π-electroncyclization (EC) to (+)-harziphilone. Alternatively, the oxacyclic ring of harziphilone could arise from zwitterions **274** by an intramolecular displacement of a neutral molecule of DABCO.



Scheme 63

Agapiou and Krische found that enoate–enone lack the necessary electrophilicity to undergo efficient cyclization. Interestingly, the thioenoate–enone substrate **276** demonstrated heightened reactivity and exquisite chemoselectivity with the catalysis of tributylphosphine to provide desired cyclized product **277** in 81% yield. Cyclohexene **277** was elaborated to the natural product ricciocarpin A (equation 154 in Scheme 64).[77a] The synthetic utility of the intramolecular RC reaction is noteworthy underscored

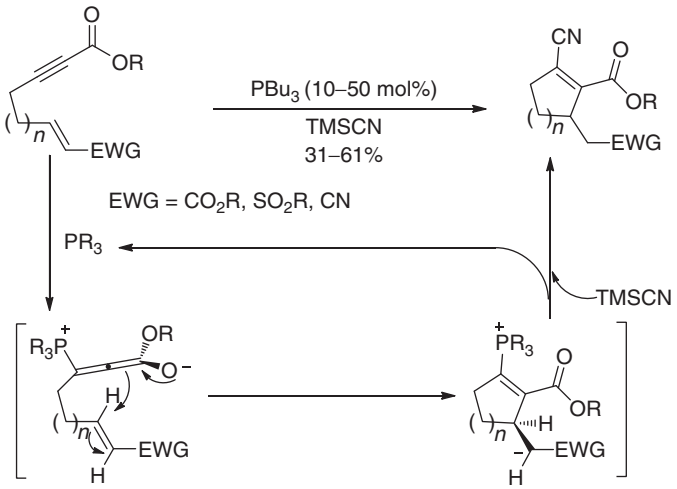


Scheme 64

by the formation of a new C–C σ bond in a densely functionalized cyclic product. Starting from the enone–enoate **278**, Roush and coworkers obtained that the desired cyclization product **279** was in 84% yield with a 6:1 diastereomeric ratio (**279**/**280**) (equation 155 in Scheme 64).[77b] The major product **279** could be further converted into antimitotic agent FR182877. One year later, Roush's group reported the total synthesis of (−)-spinosyn A via a diastereoselective transannular RC reaction. The RC ring contraction from **281** was effected with PMe_3 (8 equivalents) in *t*-amyl-OH solvent. This striking reaction proceeded with excellent

diastereoselectivity in the generation of the C3–C14 carbon–carbon bond. Desired product **283** was isolated with only minimal amounts of the C3-epimer and the olefin migration product **282** (88:7:5) (equation 156 in Scheme 64).[77c–e]

Recently, MacKay et al. reported an intramolecular Rauhut–Currier reaction utilizing alkynoates as the initial conjugate acceptor. A series of densely functionalized five- and six-membered ring products were obtained from ynoate–enoate, ynoate–enenitrile, and alkynyl sulfone–enenitrile substrates (equation 157 in Scheme 65).[78] Trialkylphosphines catalyze this reaction, and TMSCN serves as a pronucelophile to effect turnover of the catalyst and the formation of a second C–C bond. Because of the highly electrophilic alkyne acceptor, this reaction yields products that cannot be easily accessed from the traditional Rauhut–Currier reaction.



(157)

Scheme 65

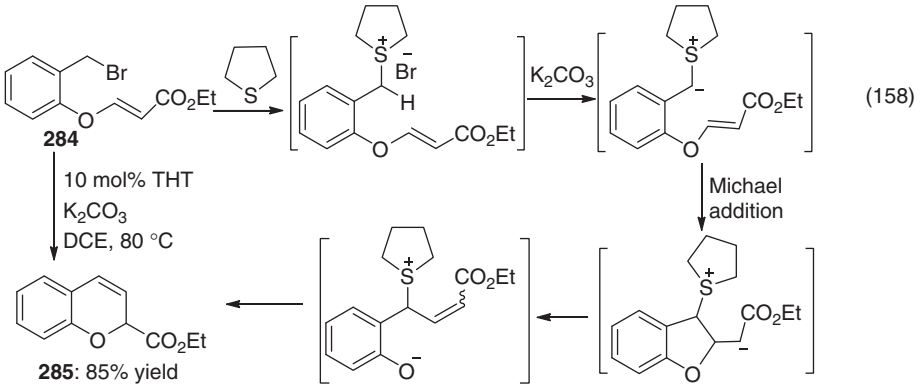
Tang and coworkers examined the sulfur ylide-initiated intramolecular Michael addition transformations. In the presence of 10 mol% tetrahydrothiophene (THT), on treatment of K_2CO_3, substrate **284** furnished 2*H*-chromene **285** in 85% yield (equation 158 in Scheme 66).[79a,b] The mechanism may proceed as follows: (1) THT reacts with substrate **284** to form sulfonium salt, which is subsequently deprotonated to generate the corresponding sulfonium ylide *in situ* and (2) an intramolecular Michael addition of the ylide to acrylate followed by a SN_2-substitution/β-elimination affords **285**. On the basis of the mechanism, the C–O cleavage involved in the β-elimination is one of the key steps to form 2*H*-chromene. When substrates **286** were used, the β-elimination step was inhibited and cyclopropanes **287** were obtained in good yields under similar reaction conditions using Cs_2CO_3 (equation 159 in Scheme 66).[79c,d]

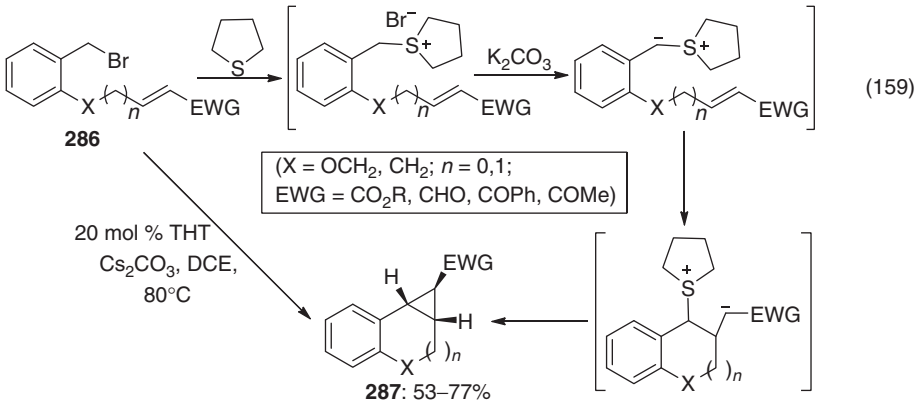
Ballini and coworkers reported the preparation of symmetrical bicyclo[3,3,1]nonanes through an anionic domino alkylation/double-Michael addition process starting from dinitroalkanes and ethyl(2-bromomethyl)acrylate. In the presence of DBU, this process allows the one-pot and highly diastereoselective synthesis of bicyclo[3.3.1]nonanes **288** in 62–82% overall yields (equation 160 in Scheme 67).[80a] Taylor and coworkers also described the intramolecular Michael addition of bicyclolactone **289** in the presence of piperidine to efficiently produce tricyclolactones **290**, which were the key intermediates for total synthesis of (+)-dictyosphaeric acid A (equation 161 in Scheme 67).[80b]

In the amine-catalyzed addition reactions, Kreis and Carreira demonstrated an intramolecular Michael addition of methyl cyclohex-3-enonecarboxylate **291** in the presence of *N*-methylbenzylamine and 4 Å molecular sieves. The adduct could be reduced by H_2/Pd providing the octahydroindene **292**, as a key intermediate for (−)-dendrobine, in high diastereoselectivity (10:1) with complete stereocontrol at C3 and C11 (equation 162 in Scheme 67).[80c] Thomson's group developed an intramolecular Michael addition of aldehydes under the catalysis of O-TMS-protected diphenylprolinol. This strategy was used to construct *trans*-substituted cyclohexane **293**, which could readily undergo Wittig reaction and another intramolecular Michael addition sequentially to afford dicyclohexanone derivatives **294** (equation 163 in Scheme 67).[80d] Dicyclohexanone **294** is the key intermediate for the total synthesis of the *Galbulimima* alkaloid (−)-GB17.

Harmata and Hong demonstrated that *o*-bromocinnamates and analogs **295** can be coupled with methyl phenylsulfoximine to construct *N*-arylsulfoximines **296** in 78–96% yields under the catalysis of $Pd(OAc)_2$. The intramolecular conjugate addition of sulfoximine carbanions to electron-deficient alkene moieties resulted in a highly stereoselective cyclization to afford benzothiazines **297** (equation 164 in Scheme 68).[81a,b] This methodology has the potential for application to the synthesis of natural product pseudopteroxazole.[81c,d]

Rodriguez and coworkers described an eco-compatible diversity-oriented synthesis of α-spirolactones or α-spirolactams. This procedure involved an olefin cross-metathesis and an intramolecular organocatalytic Michael addition-triggered spirocyclization. The β-oxo esters and derivatives **298** could be obtained efficiently by microwave-assisted olefin cross-metathesis from the corresponding homo-allyl esters and amides **299** and one equivalent of acrylonitrile in the presence of the Hoveyda–Grubbs





Scheme 66

precatalyst. The reaction mixture was directly treated with commercially available *N*-heterocyclic carbene IPr to give α-spirolactones and lactams **300** (equation 165 in Scheme 68).[82a] Nilson and Funk developed a concise diastereoselective total synthesis of (−)-nakadomarin A. Key steps included an intramolecular Michael addition/furan-*N*-acyliminium ion cascade cyclization of enecarbamate **301** in the presence of $InCl_3$ to provide the tetracyclic intermediates **302** (equation 166 in Scheme 68).[82b] Subsequent ring-closing alkyne and alkene metathese constructed the fifteen- and eight-membered azacycles, respectively.

4.01.2.2 Heteroatom Nucleophiles

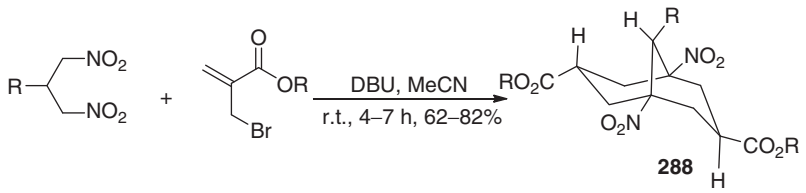
In fact, the conjugate addition with heteroatom nucleophiles was discovered earlier than the actual Michael addition. Along with the oxa-Michael addition by Loydl dating back to 1878,[83c] the aza-Michael reaction was first reported in 1874 by Heintz et al. in their work on the reaction of ammonia with acetone or mesityloxide to form diacetone-amine.[83a,b] Today, the conjugate addition of heteroatom nucleophiles to electron-deficient alkenes has been applied to the preparation of a variety of compounds with heteroatoms at the β-position of activating functional groups.[84] These additions typically occur under basic conditions, but metal- and organocatalysts, as well as enzymes, have also been shown to catalyze hetero-Michael additions. Accordingly, these addition reactions are divided into intermolecular and intramolecular processes.

4.01.2.2.1 Intermolecular additions

Heteroatom nucleophiles, such as amine, alcohol, thiol, selenide, and phosphite, to electron-deficient alkenes offer a convenient and convergent approach to prepare various heteroatom compounds. Due to space limitations only a few recent representative examples of each are presented here.

4.01.2.2.1.1 N-nucleophiles

Today, aza-Michael addition has grown into an important strategy for constructing C–N bonds in organic synthesis. A plethora of nitrogen-based nucleophiles (such as amines, oximes, carbamates, amides, azides, hydrazones, and nitrogen-containing heterocycles) and an wide range of different acceptors (such as α,β-unsaturated aldehydes, ketones, esters, amides, nitriles, nitroolefins, and vinyl sulfones) readily participate in this reaction in many different ways.



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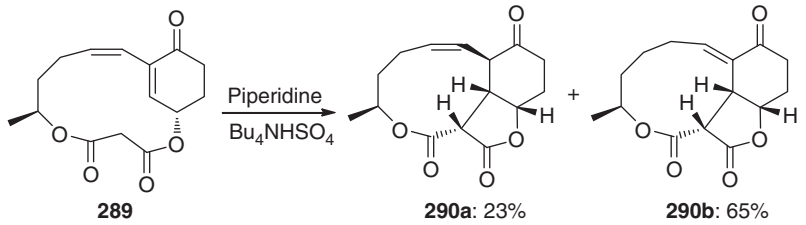

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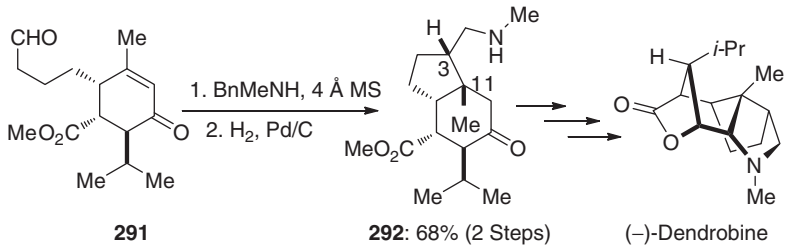

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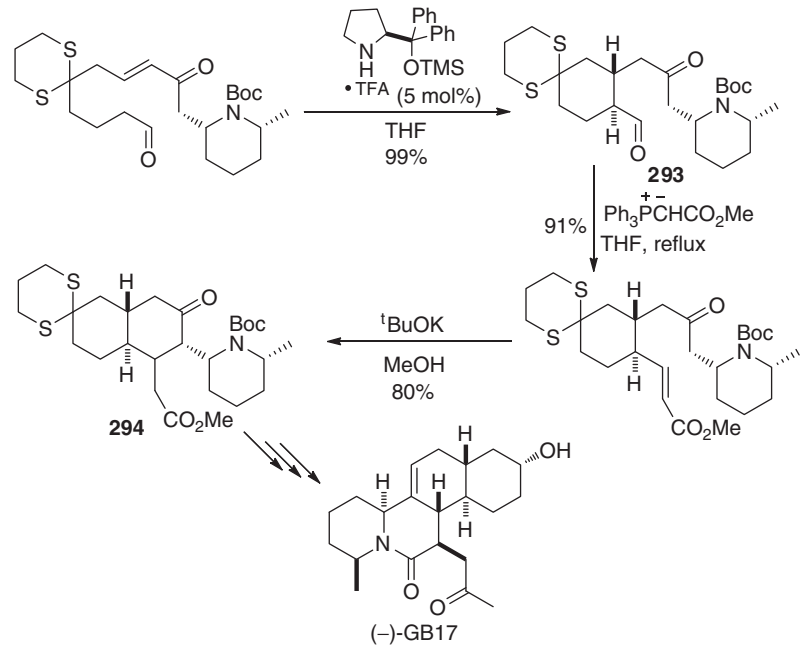
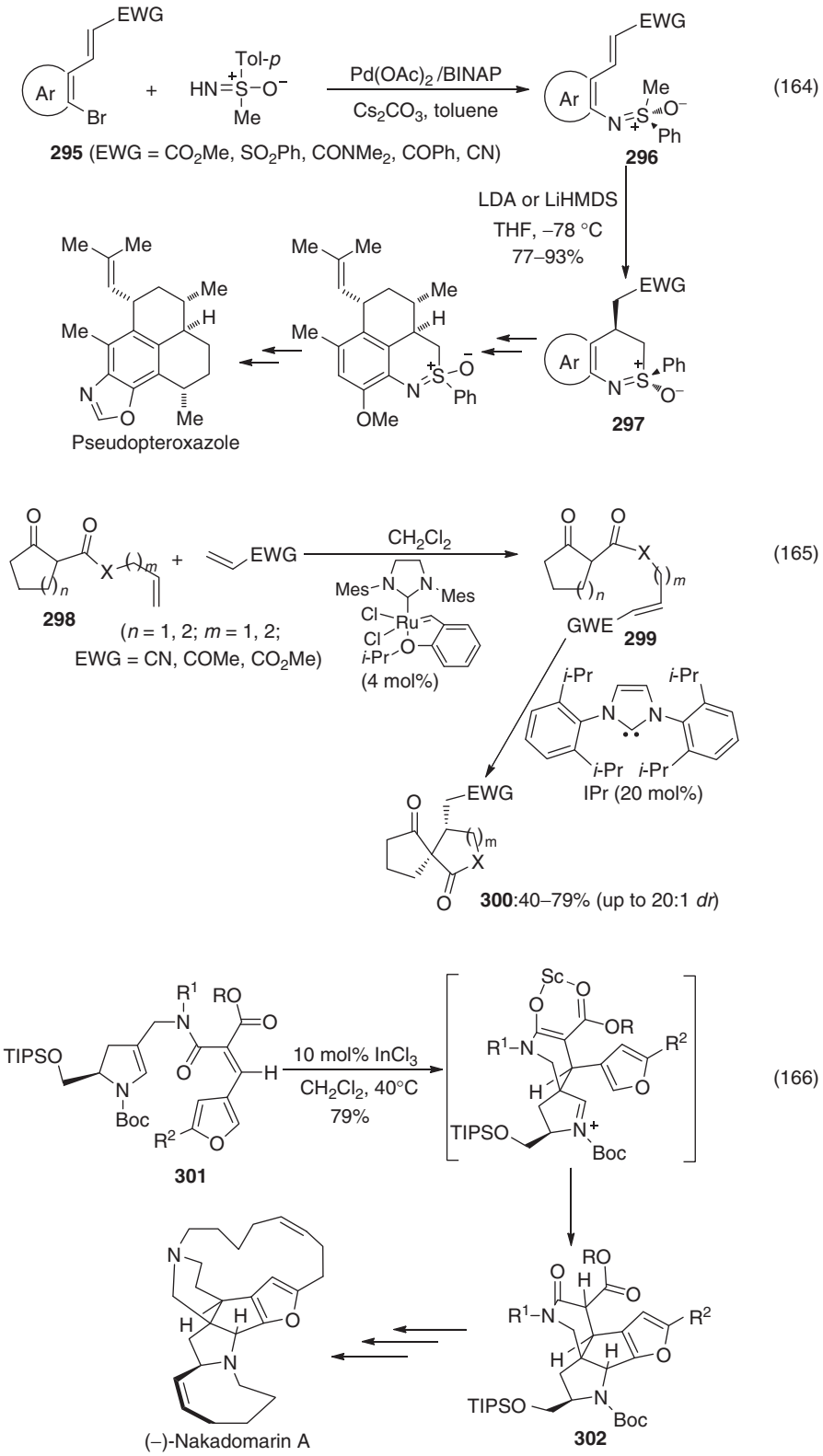


(163)

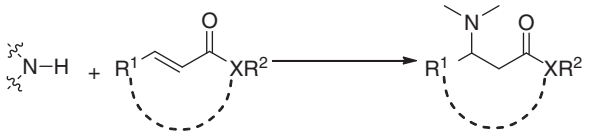
Scheme 67

β-Amino carbonyl derivatives are versatile intermediates for a large number of organic compounds, as exemplified in the preparation of amino alcohols and chiral auxiliaries. In addition, they are present as a structural unit in a variety of natural products and compounds of biological interest. Other applications of this type of compound are in the fine chemical and pharmaceutical fields. As a result of this vast range of applications, synthesis of *β*-amino carbonyl derivatives has remained an important objective over the past decade. The approach based on the conjugate addition of amines to *α*,*β*-unsaturated carbonyl compounds (aza-Michael addition) is one of the simplest and most effective methods for preparing *β*-amino carbonyl compounds. Numerous methods have been developed using a variety of promoters such as bases,[85] Lewis acids,[86] and proton acids.[87] Many environmentally friendly media have been used, among which water, ionic liquid, *β*-cyclodextrin, and polyethylene glycol are notable.[88] Additional methods



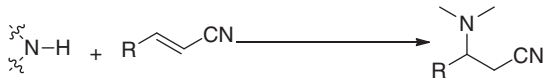
Scheme 68

including simple mixing, or grinding, or microwave-promoting addition under solvent-free conditions have also been developed.[89] Furthermore, some enzymes have demonstrated their activity for aza-Michael addition reactions in organic media, and have been used to carry out synthetic transformations.[90] These methods are really very fascinating from a synthetic chemist's point of view. Several representative examples of this large class of reactions are given in equations 167–171 in Scheme 69.



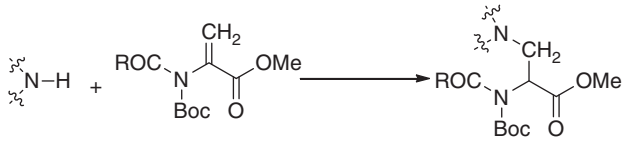
(167)

NuH: aliphatic or aromatic amines, imidazoles, carbamates
Acceptors: α,β-unsaturated ketones, esters, aldehydes, acids amides, lactones



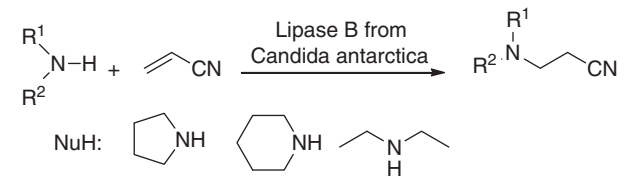
(168)

NuH: aliphatic or aromatic amines, carbamates



(169)

NuH: pyrazole, 1,2,3-triazole, imidazole, indole, pyrrole, 7-azaindole, carbazole



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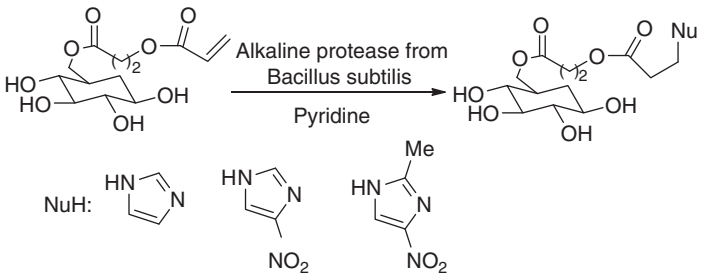
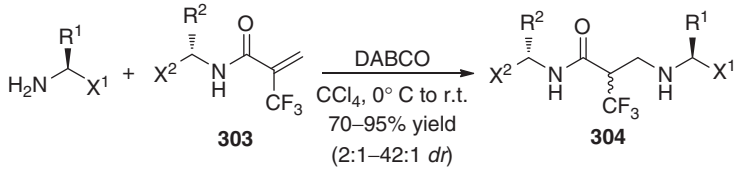


(171)

Scheme 69

Some highly functionalized compounds have been prepared through aza-Michael addition reactions. The groups of Fustero in Spain and Zanda in Italy presented a methodology for the synthesis of partially modified retro (PMR) $\Psi[NHCH_2]$ peptide mimetics **304** containing a chemically stable and stereodefined $CH_2CH(CF_3)CO$ unit. The key reaction is an aza-Michael addition of α-amino esters to *N*-(2′-trifluoromethyl)acryloyl α-amino acids **303**, which takes place in a stereoselective manner (equation 172 in Scheme 70).[91] Qu et al. developed a green, rapid, and operationally simple method for regioselective Michael addition of pyrimidine and purine derivatives **305** to acrylonitrile for the synthesis of acyclic nucleosides **306** in neat water under MWI (equation 173 in Scheme 70).[92a] Zhong and coworkers described an organocatalytic one-pot multistep transformation for the synthesis of multisubstituted *N*-hydroxypyrroles **308** by using α-carbonyl oxime compounds **307** and α,β-unsaturated aldehydes in the presence of secondary amine. This synthesis involves sequential Michael addition, intramolecular aldol condensation, and aromatization reactions through iminium activation of α,β-unsaturated aldehydes by diisopropylamine. In this procedure, carbonyl oximes acted as unusual *N*-selective nucleophiles in the Michael addition reaction (equation 174 in Scheme 70).[92b] Thomassigny and coworkers demonstrated that two polyhydroxylated piperidines **309** could be prepared in short sequences from diacetone *gluco* and allofuranose. The key step is a piezo-aza-Michael addition of diphenylmethanamine to enoates bearing a sugar moiety in the γ-position (equation 175 in Scheme 70).[93]

The addition of hydrazine to $\alpha\beta$-unsaturated aldehydes and ketones presented an efficient way to synthesize 1,3,5-trisubstituted pyrazoles **310** (equation 176 in Scheme 71).[94a–c] Starting from electron-deficient 1,3-conjugated enynes and hydrazines, Zhang's group developed a simple and efficient synthetic strategy for preparing 1,3,4,5-tetrasubsituted pyrazoles **311** via a Michael addition/unprecedented tandem cyclization/air oxidation under mild reaction conditions (equation 177 in Scheme 71).[94d] This



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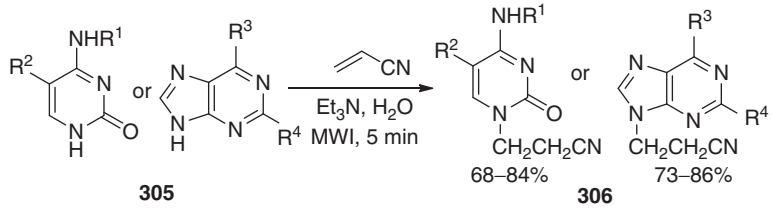

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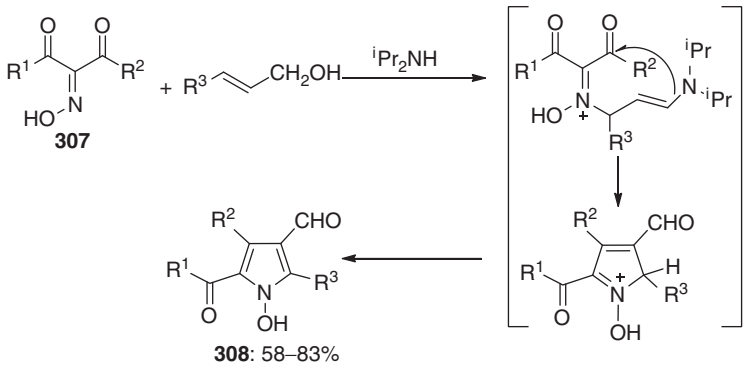

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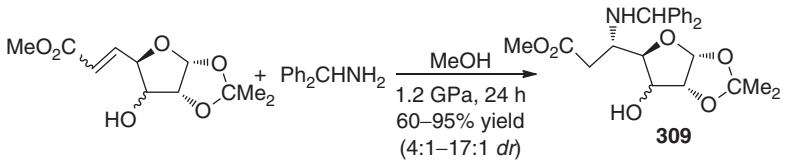


(175)

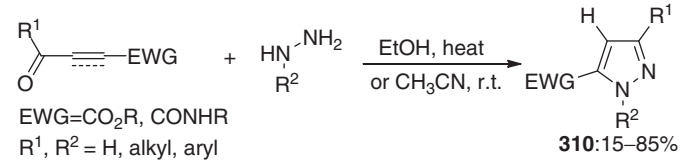
Scheme 70

methodology has potential applications in the generation of libraries of pyrazoles in pharmaceutical science. They also found that an Et_3N-catalyzed tandem reaction of electron-deficient 1,3-conjugated enynes with hydroxylamines provided rapid, metal-free, and regioselective access to highly substituted multifunctionalized 2,3-dihydroisoxazoles **312** under mild conditions. The reactions of 3-(2-arylethynyl)-4*H*-chromen-4-ones with hydroxylamines afford *β*-amino enones under the same reaction conditions (equation 178 in Scheme 71).[94e]

The conjugate addition of nitrogen nucleophiles to nitroolefins can provide nitroamine adducts (equation 179 in Scheme 72), which are readily transformed into vicinal diamines or *α*-amino acids. Kamimura et al. employed secondary acyclic formamides as nitrogen nucleophiles to nitroolefins under basic conditions to give the corresponding Michael adducts in 30–80% yields,[95a] whereas Ziyaei-Halimehjani and Saidi demonstrated an addition reaction of aromatic amines to nitroolefins in water without using any catalyst.[95b] Recently, Choudhary and Peddinti provided a catalyst-free and solvent-free green protocol for the synthesis of nitroamines through the Michael addition of amines to nitroolefins by simple mixing or grinding.[95c] In addition, nitrosoalkenes are highly reactive intermediates and can serve as attractive Michael acceptors. For example, the conjugate addition of ammonia, amines, and optically active amino esters to phosphorylated nitrosoalkenes **313** gave rise to the formation of the functionalized *α*-amino phosphorus compounds **314** (equation 180 in Scheme 72).[95d]

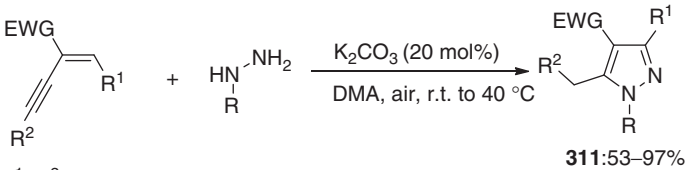
Liang et al. developed an interesting route for the synthesis of sulfonate-containing *N*-donor ligands **315** involving the conjugate addition of primary or secondary amines to sodium vinylsulfonate. These syntheses were conducted using environmentally benign methods in water and did not require harsh bases or acids (equation 181 in Scheme 72).[96a] Vinyl sulfones can also be used as Michael acceptors. For example, a fluorovinyl sulfone **316** was functionalized by addition of aliphatic, aromatic amines, and amino acid alkyl esters through an aza-Michael addition reaction. The corresponding adducts of benzothiazolyl aminosulfones **317** were employed as potential reagents for the preparation of functionalized fluoroalkylidenes through the modified Julia reaction (equation 182 in Scheme 72).[96b]

β-Aminophosphonic acids, as isosteric or bio-isosteric analogs of the corresponding amino acids, have attracted particular attention due to their diverse biological activity. The conjugate addition of amines to various vinyl phosphonates and



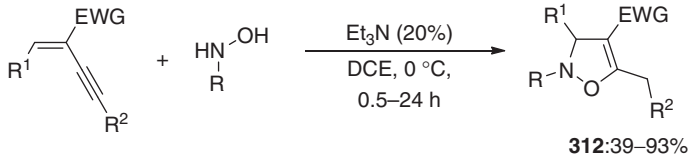
EWG=CO_2R, CONHR
R^1, R^2 = H, alkyl, aryl

(176)



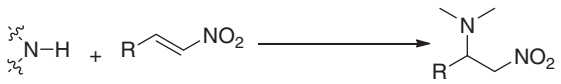
R^1, R^2 = H, alkyl, aryl; R = H, alkyl, aryl;
EWG = COMe, CHO, COAr, CO_2Me, CN

(177)



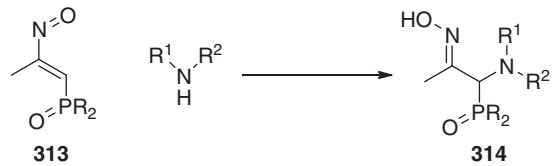
(178)

Scheme 71



(179)

NuH: aliphatic or aromatic amines, carbamates...



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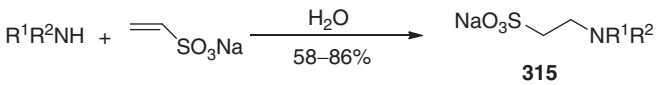

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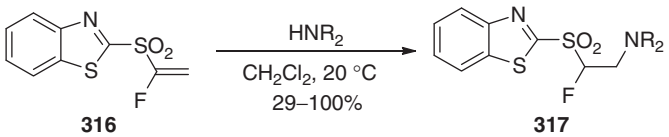
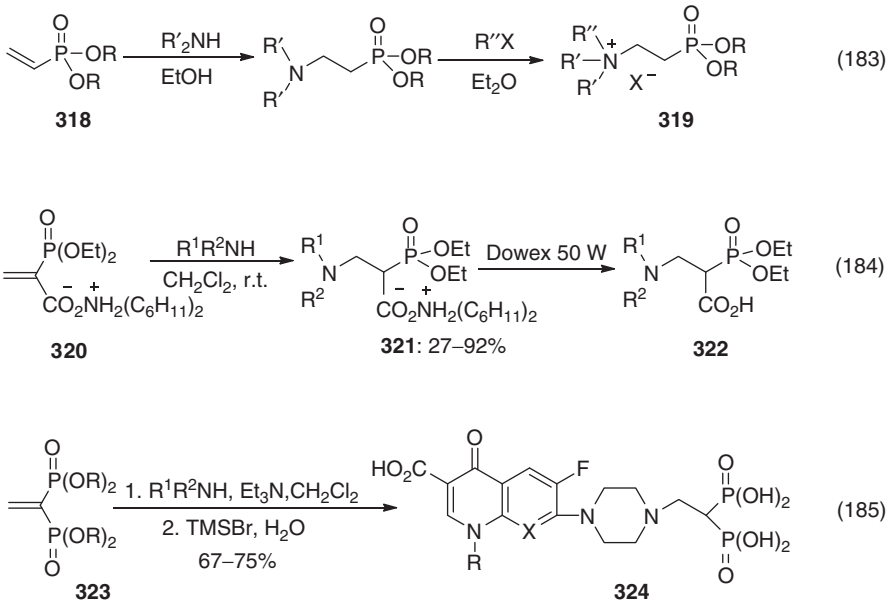


(182)

Scheme 72

phosphinates is one of the most important methods for the synthesis of β-aminophosphonic and phosphinic acid derivatives.[97a–c] For example, Floch and coworkers reported the preparation of cationic phosphonolipids **319** as synthetic nonviral vector-mediated gene transfer. The synthesis of these quaternary ammonium phosphonates took place through addition of secondary amines to vinylic phosphonate **318** and subsequent quaternization (equation 183 in Scheme 73).[97d,e] The conjugate reaction of different nitrogen nucleophiles to dicyclohexylammonium vinylphosphonate **320** afforded a series of β-aminophosphonates **321**. Ion exchange chromatography of these salts gave rise to the corresponding β-aminophosphonates **322** in nearly quantitative yields (equation 184 in Scheme 73).[97f] Several fluoroquinolone antibacterials **324** were prepared through Michael addition of



(183)

(184)

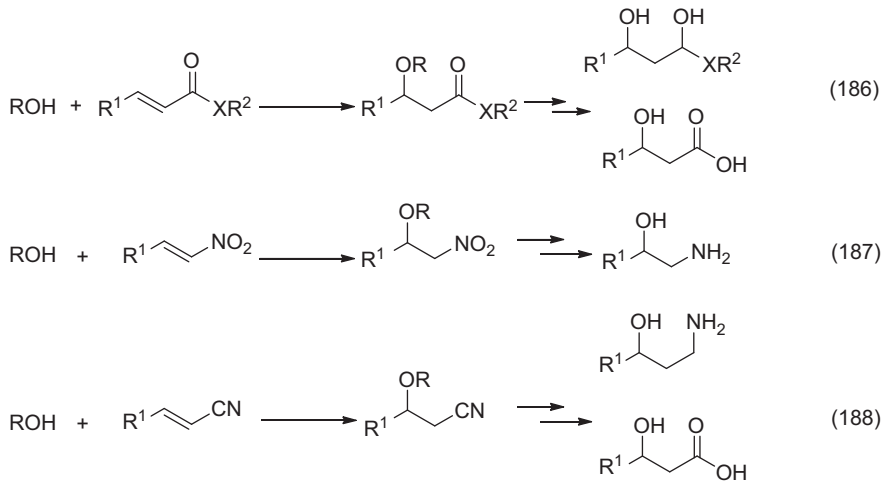
(185)

Scheme 73

aminoquinolones to ethenylidenebisphosphonate **323** in CH_2Cl_2 in the presence of Et_3N, followed by treatment with bromotrimethylsilane and subsequent hydrolysis (equation 185 in Scheme 73).[97g,h] It is noteworthy that water was also employed as solvent to accelerate the addition of amines to vinylphosphonates to yield β-aminophosphonates without any catalyst.[97i]

4.01.2.2.1.2 O-nucleophiles

Since Loydl reported the reaction of fumaric acid with sodium hydroxide for the synthesis of artificial malic acid in 1878, this reaction has been widely applied in the synthesis of 1,2-diol, 1,2-amino alcohol, β-hydroxy acid, and 1,3-amino alcohol derivatives (equations 186–188 in Scheme 74),[98] and several new versions of the reaction have recently been introduced.



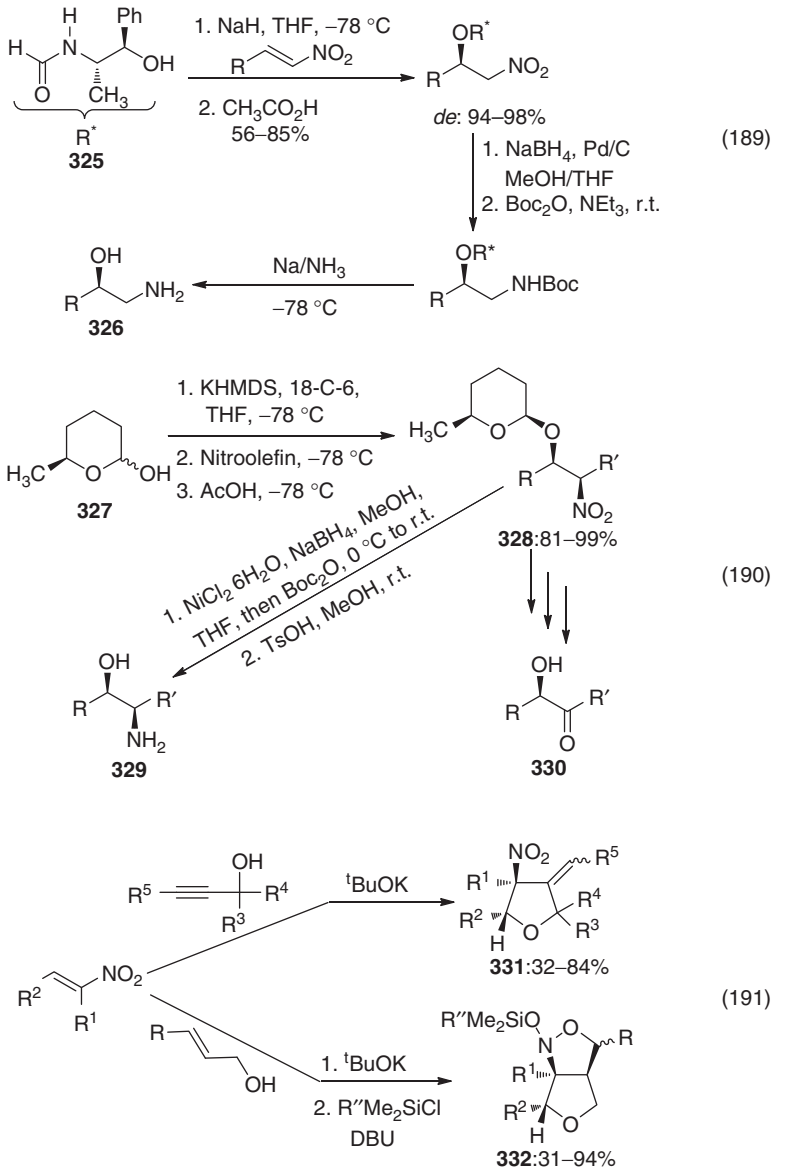
(186)

(187)

(188)

Scheme 74

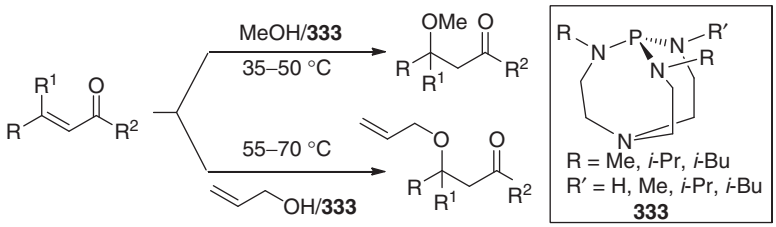
In the late 1990s, Enders' group used the sodium salt of *N*-formylnorephedrine **325** as a chiral hydroxide equivalent in reactions with aliphatic nitroalkenes for the preparation of vicinal amino alcohols **326**, and observed high diastereoselectivities (equation 189 in Scheme 75). However, when aryl nitroalkene acceptors were used, both the diastereoselectivities and the yields were low.[99] Recently, Dixon and coworkers found that the 'naked' alkoxide of 6-methyl-δ-lactol **327**, formed by deprotonation with potassiobis(trimethylsilyl)amine (KHMDS) and sequestering with [18]-crown-6, underwent highly diastereoselective oxy-Michael additions to a range of nitroalkene acceptors to give the adducts **328** in good yields. Subsequent reduction of the nitro group and the removal of the 6-methyltetrahydropyran auxiliary afforded the desired enantiomerically enriched 1,2-amino



Scheme 75

alcohols **329**. In addition, the treatment with tetrapropylammonium perruthenate gave rise to α-hydroxy ketone derivatives **330** (equation 190 in Scheme 75).[100] Bonne and coworkers reported Michael addition-initiated anionic sequences for the stereoselective preparations of a variety of highly functionalized heterocyclic compounds starting from simple nitroolefins. On reaction with propargyl or allylic alcohols, nitroalkenes acted as excellent Michael acceptors to undergo subsequent ring closure onto nonactivated alkynes or alkenes, which led to *exo*-methylene tetrahydrofuran or isoxazolidine derivatives **332** and **332** (equation 191 in Scheme 75).[101]

The addition of alcohols to α,β-unsaturated carbonyl compounds leads to the formation of intermediate enolates, which can then serve as starting points for further reactions or can be protonated to give β-hydroxy carbonyl derivatives. Verkade and coworkers demonstrated an oxa-Michael addition of alcohol nucleophiles to various α,β-unsaturated carbonyl compounds by using a proazaphosphatrane catalyst **333**. Primary and allylic alcohols are suitable substrates, as are cyclic and acyclic acceptor systems. The reaction was performed under mild conditions, and yields were good to excellent (equation 192 in Scheme 76).[102a] However, higher-order and thus more hindered alcohols are not suitable substrates for this reaction. A similar approach was developed by Bergman and coworkers. It was found that simple trialkylphosphines such as trimethylphosphine efficiently catalyze the oxa-Michael addition of primary, secondary, and aryl alcohols with various acyclic acceptors under mild conditions (equation 193 in Scheme 76).[102b] Mechanistic studies indicated that the conjugate addition of phosphine to the unsaturated carbonyl compound resulted in formation of phosphonium enolate, which deprotonated an equivalent of alcohol. The alkoxide of the ion



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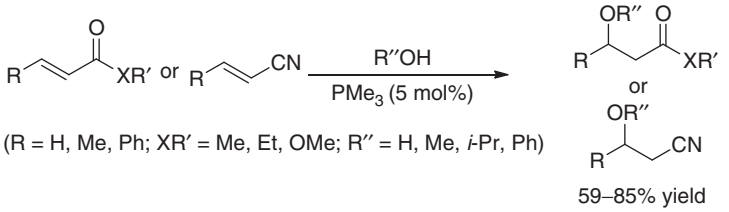
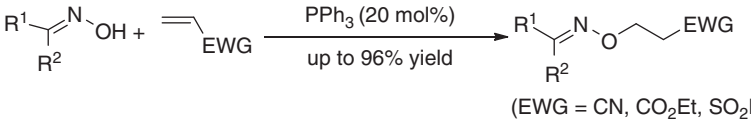


(R = H, Me, Ph; XR′ = Me, Et, OMe; R″ = H, Me, *i*-Pr, Ph)

(193)



(EWG = CN, CO_2Et, SO_2Ph)

(194)

Scheme 76

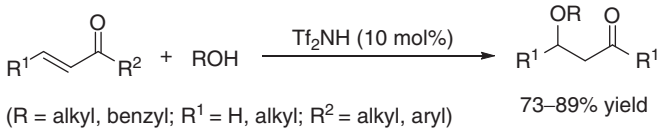
pair then underwent a subsequent conjugate addition to give an enolate ion pair. Protonation of the enolate partner gave rise to the formation of the adducts. Bhuniya et al. developed a similar protocol for the addition of oximes to different Michael acceptors.[102c] Triphenylphosphine was employed as catalyst in the oxa-Michael reaction of both aldoximes and ketoximes to a series of conjugate acceptors (equation 194 in Scheme 76). Interestingly, Hanefeld's group reported an enzyme-catalyzed Michael addition of water to conjugated carbonyl compounds. It was found that the enzyme not only catalyzes the Michael addition of water but also the *in situ* oxidation of the product.[102d]

Small organic acids and bases can also be used as catalysts in oxa-Michael reactions. For example, Wabnitz and Spencer reported an interesting conjugate addition of alkyl and benzyl alcohols to α,β-unsaturated ketones by employing bis(trifluoromethane)sulfonamide (Tf_2NH) as a strong acid catalyst (equation 195 in Scheme 77),[103a] whereas Connon and coworkers presented an amine-catalyzed hydroxyalkylation of a series of Michael acceptors that can be performed under ambient atmosphere (equation 196 in Scheme 77).[103b] The scope of these reactions in terms of substrates is comparable to the phosphine-catalyzed reactions mentioned in Scheme 76.

The combination of an oxa-Michael addition followed by an aldol condensation permits the easy construction of cyclic ketone derivatives. For example, in the presence of DABCO, the reaction of unprotected *o*-hydroxybenzaldehydes with cyclohexenone proceeded to give a series of tetrahydroxanthones **334** (equation 197 in Scheme 77).[104a] The sequence was initiated by the Michael addition of the phenol onto the cyclohexenone and a subsequent aldol condensation provided the tetrahydroxanthone. The use of 2-cyclopent-1-one furnished similar sequential products, but yields were low. Based on the synthetic access to tetrahydroxanthenones **335**, the same group accomplished the total synthesis of the fungal metabolite diversonol (equation 198 in Scheme 77).[104b]

Dialkyl vinylphosphonates can also be used as acceptors in oxa-Michael addition reactions. An addition of primary alcohols to dialkyl vinylphosphonates has been reported using strong bases[105a,b] or carbonates at elevated temperature.[105c] Janeba and coworkers described an oxa-Michael addition of various secondary and branched primary alcohols to diethyl vinylphosphonate under mild reaction conditions (equation 199 in Scheme 78).[105d] A series of adducts were obtained in moderate-to-good yields. However, an analogous treatment of acyclic nucleoside alcohols afforded the desired phosphonoethylated products **336a–c** in poor yields (12–14%), due to the low solubility of the starting compounds in *t*-BuOH and the presence of the reactive amino group in the C-6 position of the purine ring.

Multicomponent reactions triggered by conjugate additions can be applied to the preparation of highly functionalized compounds. Zhang's group developed the palladium-catalyzed multicomponent reactions of electron-deficient enynes and nucleophiles with allyl or aryl halides.[106] The key step in this synthetic endeavor was an intermolecular oxa-Michael reaction between α-alknyl α,β-unsaturated carbonyl compounds and alcohols. Subsequent intramolecular cyclization and cross-coupling with allyl halides gave tetrasubstituted furan products **337**. Direct cross-coupling with aryl halides led to tetrasubstituted allene derivatives **338** (equations 200 and 201 in Scheme 79).



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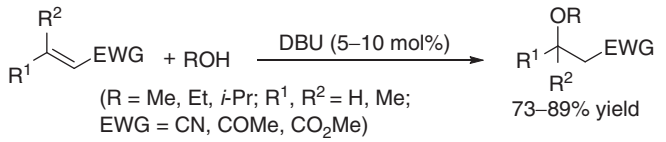

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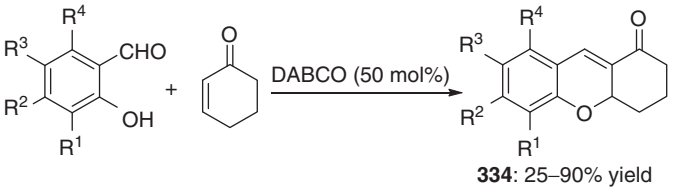

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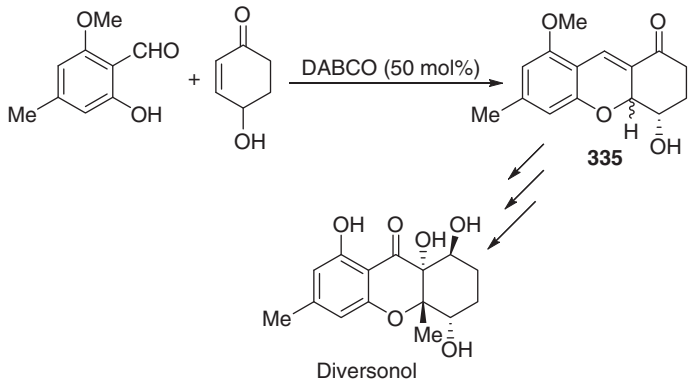
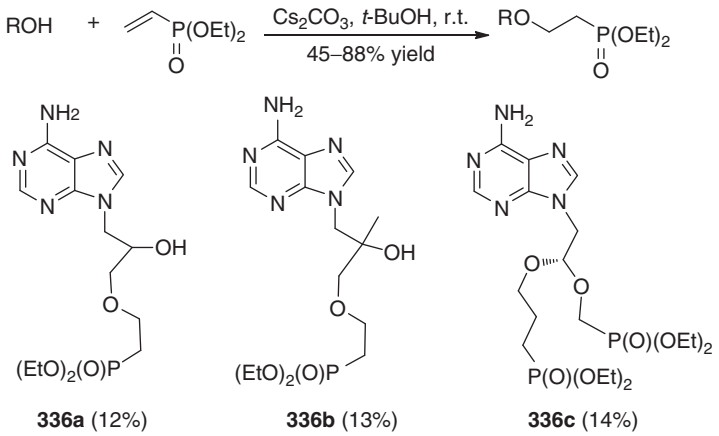


(198)

Scheme 77

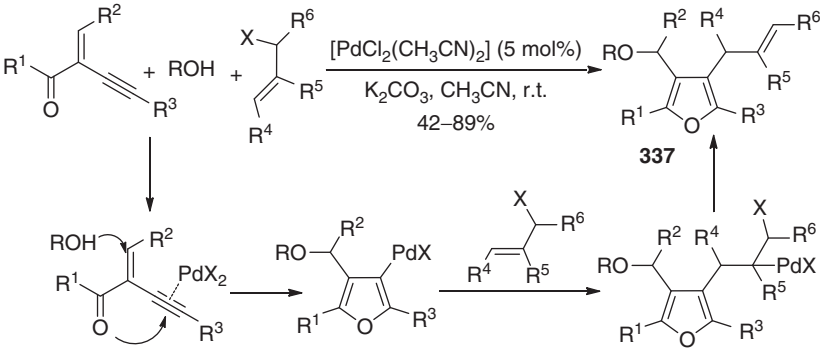


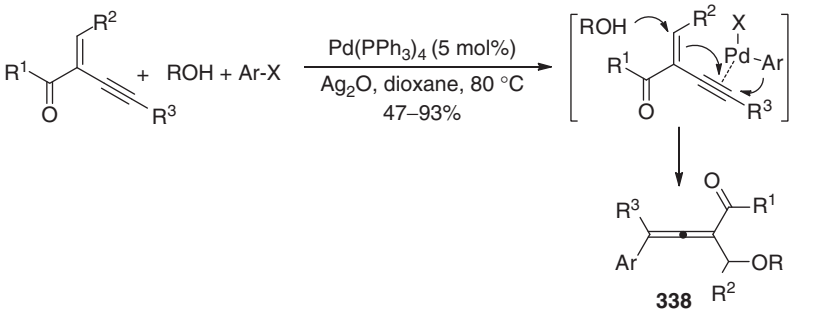
(199)

Scheme 78

4.01.2.2.1.3 S- and Se-nucleophiles

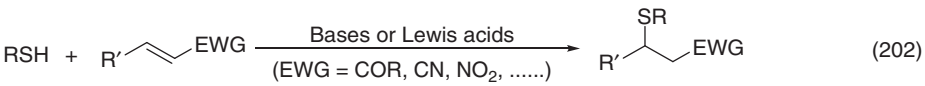
Sulfur-containing organic compounds are widely present in nature and have commercial significance.[107] The thia-Michael addition is one of the most versatile and practical reactions for C–S bond formation in organic synthesis. Many methods are mainly focused





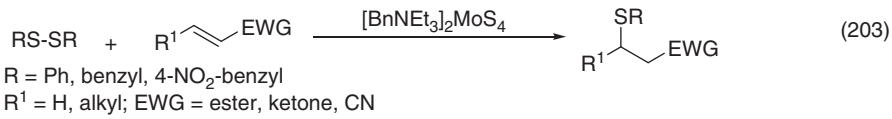
Scheme 79

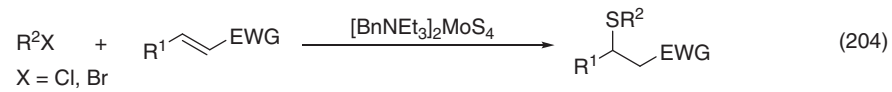
on the use of basic and acidic (including Lewis acids) catalysts for the direct addition of thiols to Michael acceptors under homogeneous or heterogeneous conditions (equation 202 in Scheme 80).[108] However, recently efforts have been made to introduce new methodologies that are efficient and more compatible with the environment. To achieve this goal, the reactions conducted under solvent-free conditions,[109] in ionic liquids,[110] and using water as the medium,[111] have been reported.



Scheme 80

To avoid the use of highly volatile and foul-smelling thiols, several odorless protocols have also been reported. Disulfide compounds can be used as thiol equivalents for the conjugate addition of S-nucleophiles. Chandrasekaran and coworkers demonstrated that benzyltriethylammonium tetrathiomolybdate can not only cleave the disulfide bond, but can also promote the intermediate generated *in situ* to undergo a facile conjugate addition to Michael acceptors (equation 203 in Scheme 81).[112a] Interestingly, in the presence of tetrathiomolybdate and alkyl halides as well as Michael acceptors, a three-step tandem transformation, involving sulfur transfer, reduction of disulfide, and conjugate addition, can proceed to give the corresponding adducts in high yields (equation 204 in Scheme 81). In addition, InI,[112b] Zn/$AlCl_3$,[112c] and PPh_3[112d] can also promote the cleavage of

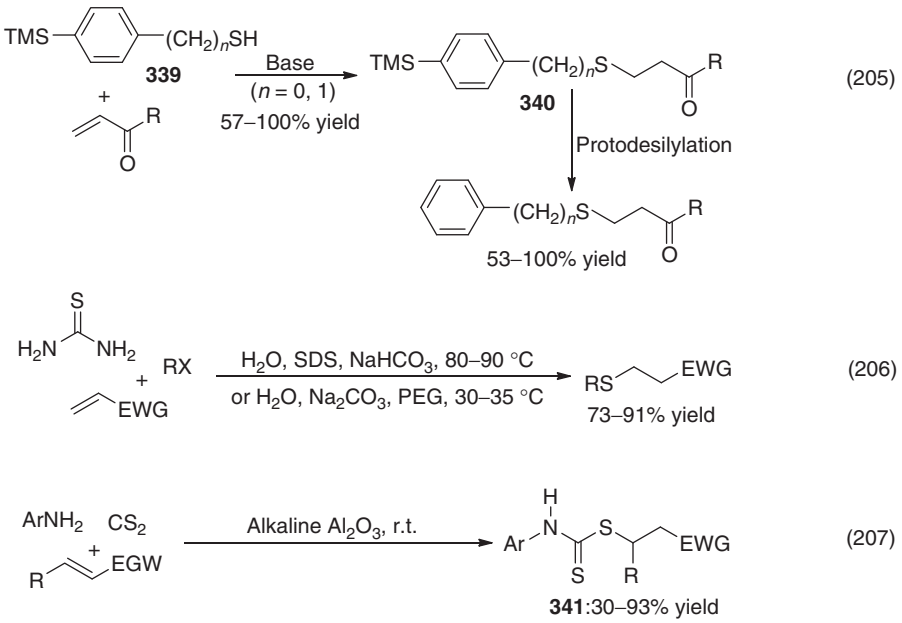




Scheme 81

dialkyl disulfides generating thiolate anions, which then undergo conjugate addition to α,β-unsaturated ketones, aldehydes, carboxylic esters, and nitriles under neutral conditions.

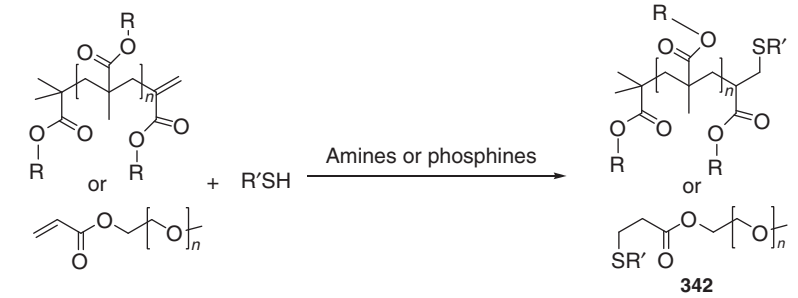
Silylated benzyl mercaptan and benzenethiol **339** are useful as faintly malodorous or even odorless synthetic equivalents of the parent thiols. In the Michael addition of α,β-unsaturated carbonyl compounds, TBAF in THF successfully catalyzed the Michael addition of *para*-trimethylsilylated benzyl mercaptan, whereas triethylamine or DBU in petroleum ether catalyzed the reaction of *para*-trimethylsilylated benzenethiol. Protodesilylation of the Michael adducts **340** with trifluoroacetic acid permitted the introduction of the benzylthio and phenylthio groups under odorless reaction conditions (equation 205 in Scheme 82).[113a] Thiourea can also serve as the S-source for the *in situ* generation of thiol with alkyl halides in a micellar solution of sodium dodecyl sulfate in the presence of $NaHCO_3$ or Na_2CO_3 in wet polyethylene glycol (PEG 200). An efficient and odorless synthesis of thia-Michael adducts by the addition reaction to structurally diverse electron-deficient alkenes (ketones, esters, and acrylonitrile) (equation 206 in Scheme 82). The yields of the products are good to excellent and the method is applicable to large-scale operation.[113b,c] In addition, Li and coworkers developed an efficient method for the preparation of dithiocarbamic acid esters by Michael addition of electron-deficient alkenes with amines and CS_2 in solid media alkaline Al_2O_3. A wide range of amines, especially aryl amines, reacted with CS_2 and an array of Michael receptors to afford the Michael addition products **341** in high yields (equation 207 in Scheme 82).[114]



Scheme 82

Thiol-Michael addition reactions between thiols and activated ene groups have been largely studied as metal-free 'click' reactions to synthesize a range of macromolecular structures.[115] These reactions are usually performed using organic phosphines or amines as co-reagents. For example, Haddleton and coworkers described a thiol–ene Michael addition reaction of a range of thiols with dimers and oligomers of some (methyl)acrylates by using different catalysts, including primary, tertiary amines, and phosphines. These reactions were performed on monomers, dimers, and oligomers to form various end functional polymers **342** (equation 208 in Scheme 83).[115h,i] Lupton and coworkers developed a divergent method for the synthesis of a [G4]-ene$_{24}$ dendrimer from [G1]-ene$_3$**343**. A phosphine-catalyzed thiol-Michael addition was used to introduce a branching diol to afford the adduct [G1]-ol$_6$**344** (equation 209 in Scheme 83).[115j] Auclair and coworkers reported the use of sulfonamide- and phosphonate-linked aminoglycoside–coenzyme A (CoA) conjugates **347** and **348** as structural and mechanistic probes for aminoglycoside *N*-6′-acetyltransferases. The key step in this synthetic endeavor was an intermolecular thiol-Michael reaction between expensive coenzyme A with vinylsulfonamide **345** or vinylphosphonate **346** in water (equation 210 in Scheme 83).[115m,n]

Organoselenium compounds are of considerable interest because of their involvement as key intermediates in organic synthesis, and much effort is being devoted to the synthesis of these compounds.[116] The conjugate addition of selenolates represents a convenient procedure to introduce a selenium-containing functionality into electrophilic organic substrates (equation 211 in Scheme 84). These addition reactions proceeded by the *in situ* formation of benzeneselenol from diphenyl diselenide in the presence of catalysts such as La/I_2,[117a] In/Me_3SiCl,[117b] and Zn/$RuCl_3$,[117c] or by using ceric(IV) ammonium nitrate in a radical process.[117d] In addition, PhSeH[117e] and PhSeZnCl[117f] can be directly used for the Michael addition in aqueous media. A variety of synthetically useful β-seleno derivatives can be obtained in good yields.



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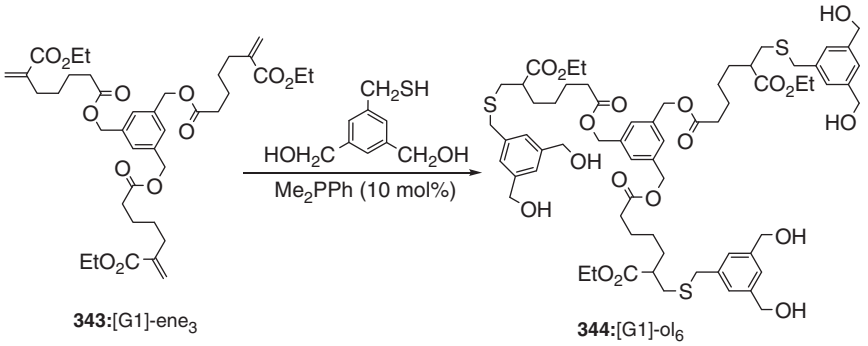

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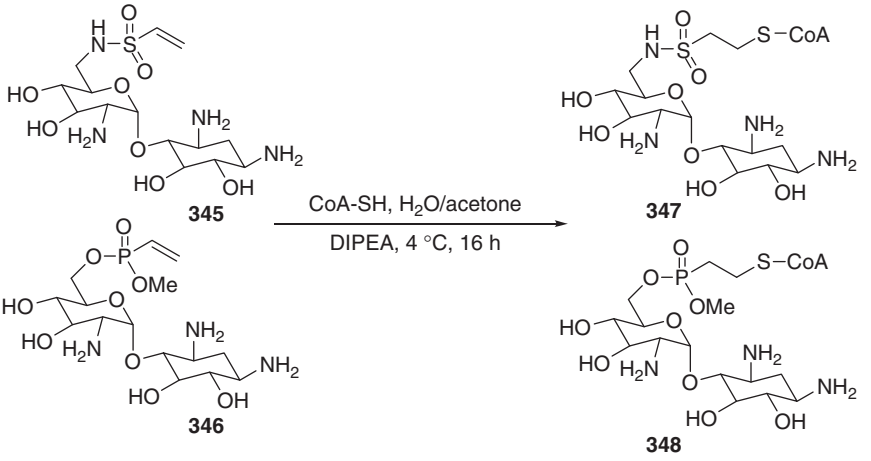
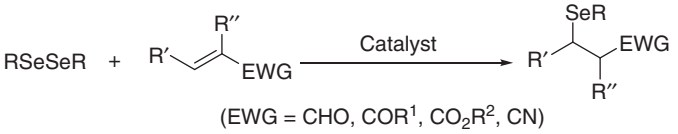


(210)

Scheme 83



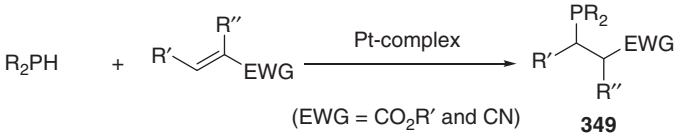
(211)

Scheme 84

4.01.2.2.1.4 P-nucleophiles

Organophosphorus compounds have received considerable attention and become the focus of intense research efforts due to their wide applications to the life science fields, agrochemistry, and material science. Apart from the well-known Michaelis–Arbuzov and Michaelis–Becker reactions, the phospha-Michael (*P*-Michael) addition is one of the most important tools for the synthesis of organophosphorus compounds through the P–C bond formation. Related subjects have been addressed in many reviews.[118] Therefore, this section will highlight recent advances in the phospha-Michael addition.

Pringle and coworkers reported a Pt-catalyzed hydrophosphination of activated olefins including acrylonitriles and acrylates (equation 212 in Scheme 85) by using R_2PH.[119] A series of adducts **349** were prepared in good yields. After P–H oxidative addition, P–C bond formation occurred by selective insertion of the olefin into the Pt–P bond. Reductive elimination formed the product and regenerated the catalyst. Based on this research, Glueck's group attempted to trap the proposed carbanion with another electrophile and developed a Pt-catalyzed three-component coupling of secondary phosphines, *tert*-butyl acrylate, and aldehydes, yielding the functionalized phosphines **350** (equation 213 in Scheme 85).[120]



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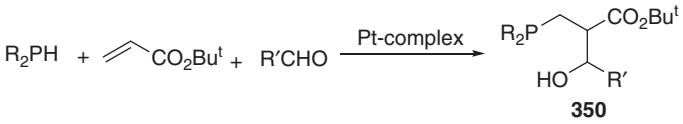
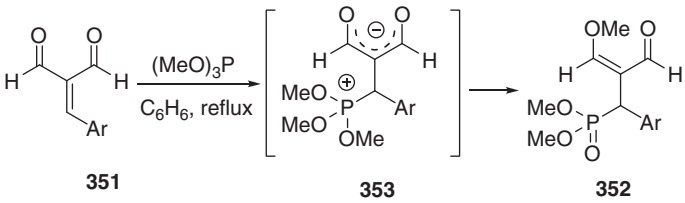


(213)

Scheme 85

Another interesting class of nucleophiles are trivalent phosphorus compounds of the general structure $(RO)_3P$. Reaction of the (arylmethylene) malonaldehydes **351** with trimethyl phosphite gave the methoxyacroleins **353** in moderate-to-good yields. This reaction can be envisaged to proceed via an Arbuzov-type rearrangement (intra- or intermolecularly) of the intermediate betain **352** (equation 214 in Scheme 86).[121a] Röschenthaler and coworkers presented similar results. The addition of trimethyl phosphite to (*E*)-1,1,1-trifuoro-4-phenyl-but-2-ene-4-one afforded the intermediate **354** as a sole product, which on hydrolysis was transformed into the fluoroalkyl-containing γ-ketophosphonate **355** (equation 215 in Scheme 86).[121b]



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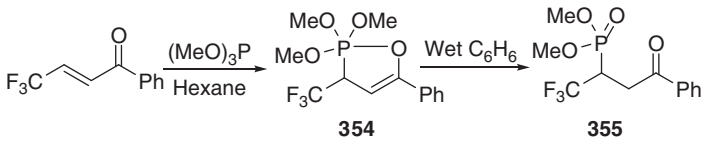
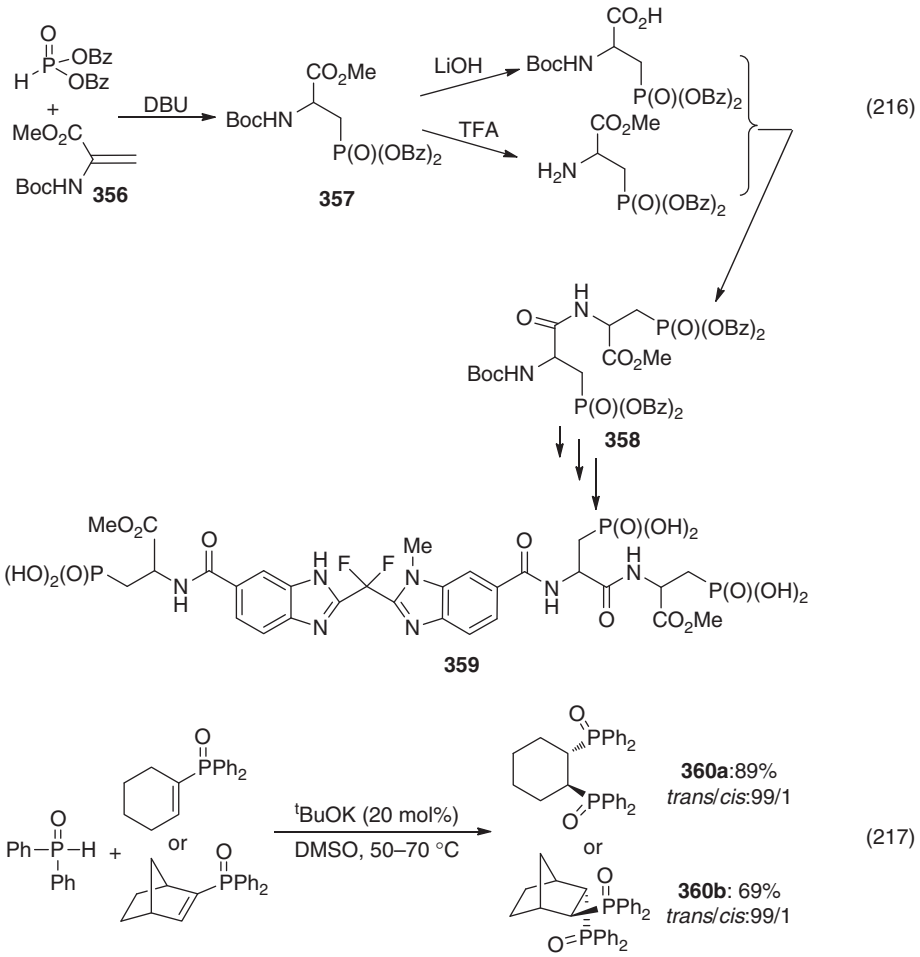


(215)

Scheme 86

Unlike in the preceding examples, the Michael addition of an $R_2P(O)H$ group is normally conducted under basic conditions – either in the presence of a basic catalyst or by using a stoichiometric amount of a strong base. For example, the reaction of dehydroalanine **356** with $HP(O)(OBn)_2$ in the presence of DBU gave orthogonally protected phosphonoalanine **357**, and ester cleavage afforded the acid, which was coupled into the bisphosphonoalanine **358** (equation 216 in Scheme 87).[122a] Introduction of bisbenzimidazole moiety and subsequent transformations gave rise to potent nonpeptidic inhibitors **359** of the hepatitis C virus (HCV) serine protease. Bunlaksananusorn and Knochel showed that KO^{t}Bu (20 mol%) promoted the addition of diphenylphosphine oxide to Michael acceptors. 1,2-Diphosphine oxides **360** can be easily prepared by this method (equation 217 in Scheme 87).[122b] Interestingly, Stockland et al. developed a microwave-assisted addition of $R_2P(O)H$ to electron-deficient terminal alkenes without solvent or additional catalyst. In many cases, the resulting adducts were obtained (>95% pure) when removed from the microwave.[122c]



Scheme 87

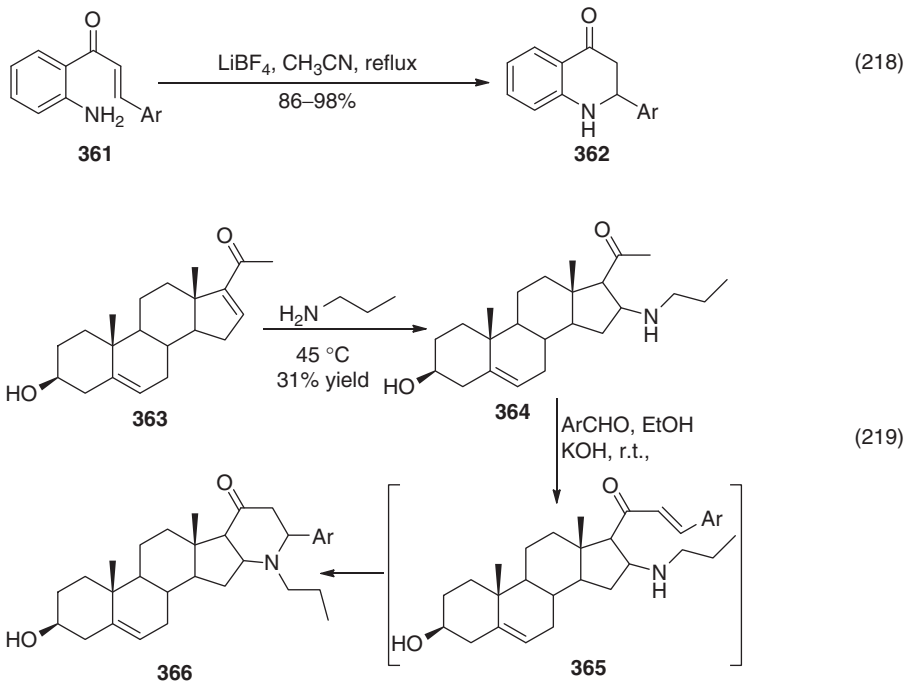
4.01.2.2.2 Intramolecular additions

4.01.2.2.2.1 N-nucleophiles

Despite the remarkable success of intermolecular aza-Michael addition reactions, intramolecular Michael addition has been developed relatively slowly. For instance, lithium tetrafluoroborate was demonstrated to be an efficient catalyst in the intramolecular aza-Michael addition of 2′-amino chalcones **361**. A series of 2-aryl-2,3-dihydroquinoline-4(1*H*)-ones **362** were prepared in high yield and purity (equation 218 in Scheme 88).[123a] Maurya and coworkers found that the syntheses of amine analogs **364** of pregnenolone were accomplished through intermolecular aza-Michael addition reaction of 16-dehydropregnenolone **363** with various aromatic and aliphatic amines. These amines were then subjected to the aldol condensation reaction with various aromatic aldehydes in ethanol using KOH as a base at room temperature to afford the condensed products **365**, which on intramolecular aza-Michael addition reaction afforded the adducts **366** (equation 219 in Scheme 88).[123b]

One-pot multistep transformations mediated by intramolecular aza-Michael addition have been successfully applied in the synthesis of various nitrogen-containing heterocyclic compounds. In 2008, Trost et al. developed a tandem ruthenium-catalyzed redox isomerization/intramolecular aza-Michael addition reaction for the synthesis of pyrrolidines and piperidines. Reaction of TsNH- and BocNH-substituted propargyl alcohols **366** with catalytic amounts of the ruthenium complex, in the presence of indium triflate and camphorsulphonic acid (CSA), directly provided a variety of differently substituted pyrrolidine and piperidine derivatives **367** (equation 220 in Scheme 89).[124a] Taniguchi's group reported one-pot synthesis of heterocycles **368** by iron-mediated halonitration of ω-alkenylamine derivatives and subsequent elimination followed by intramolecular nitro-Michael addition (equation 221 in Scheme 89),[124b] whereas Priebbenow et al. developed a one-pot three-component reaction of 2-bromophenethylsulfonamide and acryloyl chloride with various primary and secondary amines. Following the *in situ* generation of an acrylamide, a domino process, involving intermolecular Heck reaction and subsequent intramolecular aza-Michael addition, afforded the functionalized tetrahydroisoquinolines **369** (equation 222 in Scheme 89).[124c]

Stockman and coworkers provided a method for the concise total synthesis of histrionicotoxin (HTX, **371**), an alkaloid isolated from the skin extracts of frogs, in 10 steps with 19.2% overall yield or nine steps with 16.5% overall yield. An important dinitrile



Scheme 88

intermediate **370** was prepared in one pot through a tandem oxime formation/ aza-Michael addition/1,4-prototopic shift/[3+2]-cycloaddition (equation 223 in Scheme 90).[125]

4.01.2.2.2.2 O-nucleophiles

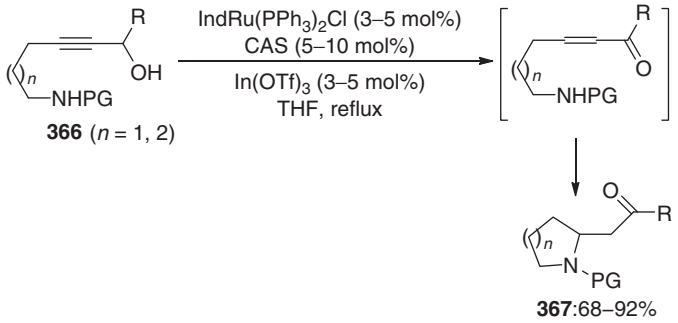
In contrast to intermolecular oxa-Michael reactions, intramolecular versions have been far from well established, especially within the context of one-pot multistep transformation and natural product synthesis. This is mainly due to the fact that reversibility and a lack of reactivity in the nucleophiles can be overcome more easily by tethering both reactants.

The intramolecular oxa-Michael addition reaction has been used to great effect for the construction of functionalized tetrahydropyran units. Both the Roush[126a] and Paterson[126b] groups constructed the F ring of spongistatin-1 by cyclizing a hydroxy group onto α,β-unsaturated esters **372** or ketones **374**. The cyclization could be promoted under basic conditions and the desired adducts (**373** and **375**) were generated in excellent diastereoselectivity (equations 224 and 225 in Scheme 91). Pattenden and Plowright described a synthesis of the C3–C19 bis-tetrahydropyran portion of phorboxazole A. In this context, an oxy anion intramolecular Michael addition proceeded to produce a *cis*-etrahydropyran ring **376** (equation 226 in Scheme 91).[126c] The A-ring **377** of (+)-ambruticin S was formed under a base-promoted thermodynamic cyclization of a hydroxy group onto an α,β-unsaturated ester (equation 227 in Scheme 91).[126d]

Based on the Maitland–Japp reaction[127] (Knoevenagel/Michael addition cascades) (equation 228 in Scheme 92), Clarke's group presented a one-pot multistep reaction for the diastereoselective synthesis of highly substituted tetrahydropyran-4-ones. The aldehyde was subjected to a Lewis acid-catalyzed aldol reaction with Chan's diene **378**, to give the expected aldol product **379**, which underwent a Knoevenagel reaction *in situ* with a second equivalent of different aldehyde, which was added to the reaction vessel. The Knoevenagel reaction was immediately followed by an oxy-Michael addition to yield the desired adducts **380** (equation 229 in Scheme 92).[128a–c] The same group accomplished an expedient total synthesis of the antibiotic natural product centrolobine **382** through this one-pot multistep transformation strategy. In this case, the undesired *trans* isomer could be reequilibrated to a 2:1 *cis*/*trans* mixture, and thus the yield of the desired 2,6-*cis* isomer **381** rose to 82% (equation 230 in Scheme 92).[128d,e]

Recently, Clarke and coworkers provided a one-pot, multicomponent asymmetric version of the Maitland–Japp reaction and applied it to the synthesis of the C1–C19 bis-pyran unit of phorboxazole B. The key pyran rings **383** were constructed by means of an asymmetric Maitland–Japp reaction involving an intramolecular oxa-Michael addition (equation 231 in Scheme 93).[128f–h]

Some Brønsted acids can be used as organocatalysts in the intramolecular oxa-Michael addition reactions. Rizzacasa and coworkers reported the total synthesis of the myxobacteria metabolite (−)-apicularen A. The key step involved an acid-mediated intramolecular oxa-Michael addition of the C13 hydroxyl into the α,β-unsaturated ketone **384** to afford *trans*-pyranone **385** as the major product (>10:1 selectivity) in 90% yield (equation 232 in Scheme 94).[129b] It was necessary to use elevated temperatures for



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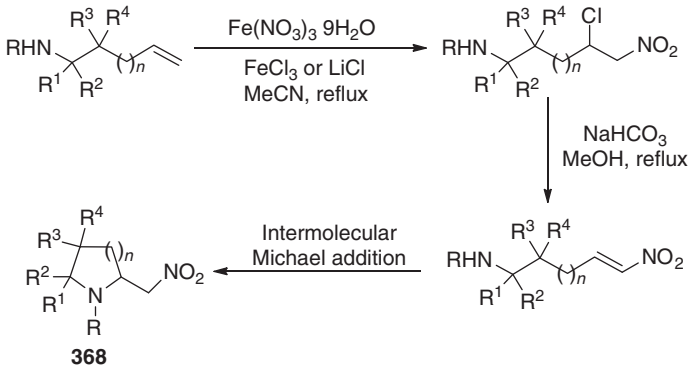

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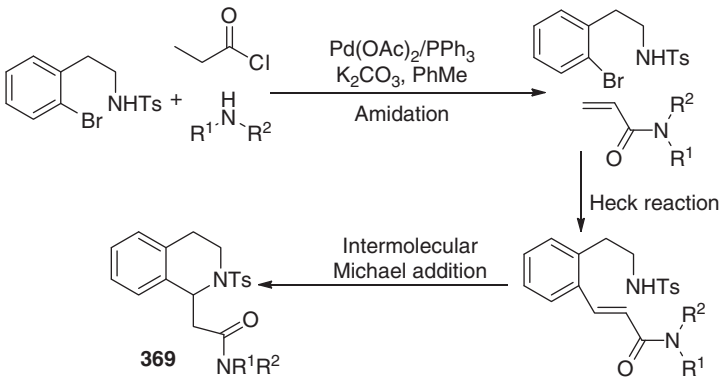
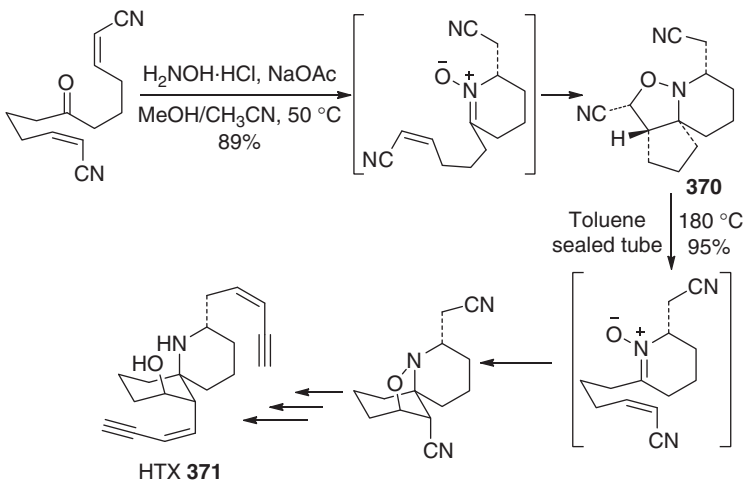


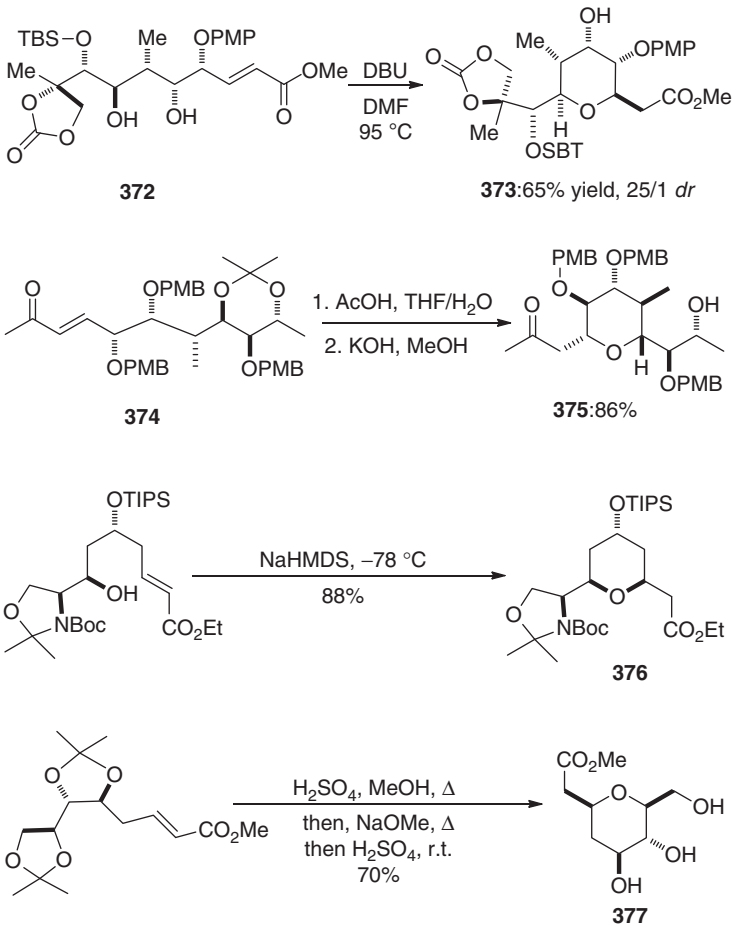
(222)

Scheme 89



(223)

Scheme 90

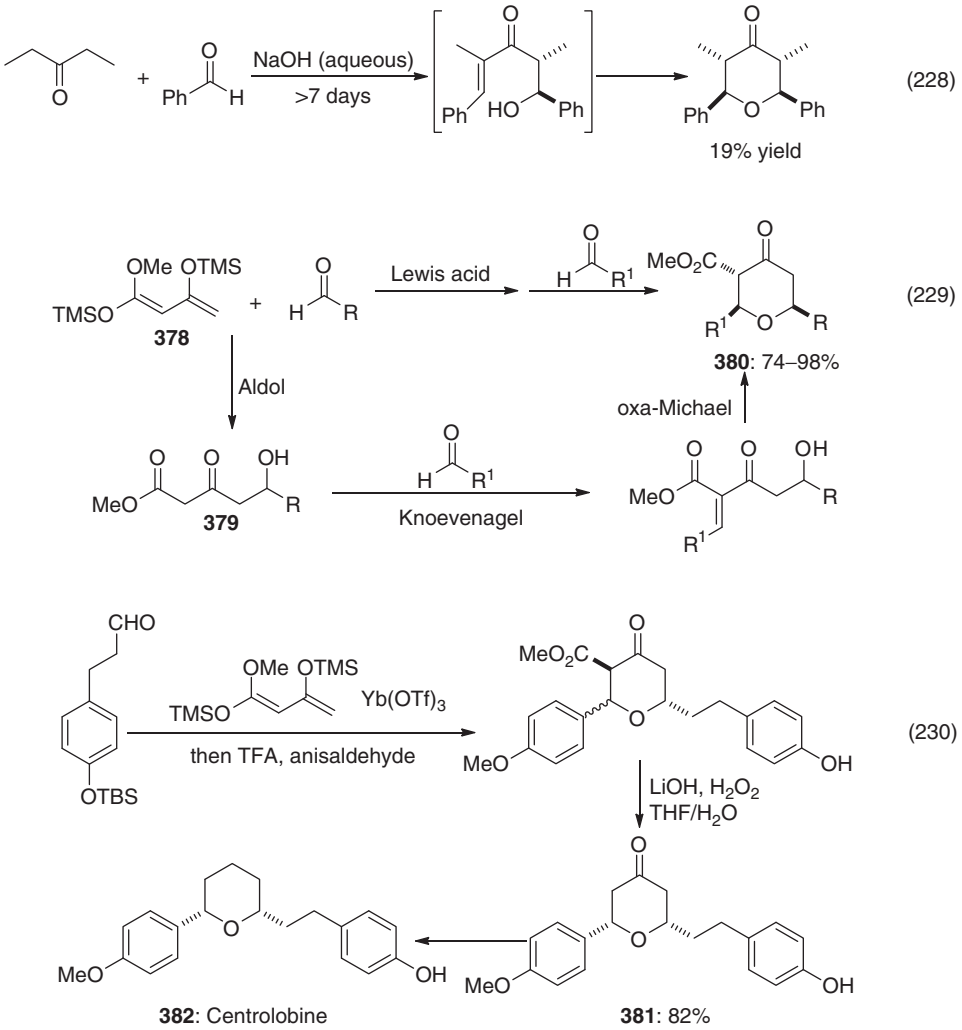


Scheme 91

this cyclization, as at lower temperatures the undesired *cis*-diastereomer was formed in 67% yield.[129a] The bicyclic core **386** of cryptocaryolone has been synthesized by a Brønsted acid-mediated oxa-Michael cyclization (equation 233 in Scheme 94).[129c] Another example is the synthesis of (−)-centrolobine by the use of an oxa-Michael reaction. The starting material enone **387**, constructed by an allylation/olefin metathesis/Horner–Wittig transformation, was cyclized by treatment with HF–pyridine under reflux to yield the thermodynamically more favorable 2,6-*cis*-tetrahydropyran ring **388** (equation 234 in Scheme 94). The carbonyl group and the benzyl ether were removed by the action of Pd/C, H_2, and HCl.[129d]

Apart from basic and Brønsted acidic catalysts, some Lewis acids and metal complexes are also suitable catalysts for intramolecular oxa-Michael addition reactions. Gouverneur and coworkers demonstrated that structurally diverse *β*-hydroxyenones **389** underwent nonoxidative 6-*endo-trig* ring closure to form highly substituted tetrahydropyranones **390** (equation 235 in Scheme 95).[130a] Amberlyst-15, $Al(ClO_4)_3{\cdot}9H_2O$, and $[Pd(MeCN)_4](BF_4)_2$ were found to be suitable catalysts for these intramolecular oxa-Michael additions. The use of $[Pd(MeCN)_4](BF_4)_2$ was particularly effective, as this palladium-mediated reaction was under kinetic control and generated tri- and tetrasubstituted tetrahydropyranones with high levels of diastereocontrol. Fürstner's group reported a Suzuki cross-coupling of homoallylic alcohols and iodoenones by using (dppf)$PdCl_2$ to access *α,β*-unsaturated hydroxyketones, which cyclized via an intramolecular oxa-Michael addition to give *cis*-2,6-disubstituted tetrahydropyrans **391** in one pot (equation 236 in Scheme 95).[130b] Fuwa et al. developed a domino olefin cross-metathesis/intramolecular oxa-Michael addition by using the Grubbs second-generation catalyst, and the reaction of alkenols and enones proceeded to give tetrahydropyrans **392** (equation 237 in Scheme 95).[130c] This strategy was also used in the natural product total synthesis.[130d,e] Wohland and Maier showed that metal cations such as Au(I) or Pt(II) can promote a tandem Meyer–Schuster rearrangement/intramolecular oxa-Michael addition of heptyn-6-yne-1,5-diols producing *cis*-2,6-tetrahydropyrans **393** (equation 238 in Scheme 95).[130f]

The compatibility of the metal-catalyzed oxa-Michael methodology with highly functionalized substrates underlines the importance of these reactions as a powerful tool for carbon–oxygen bond formation, even within complex molecules. Trost's group described a chemoselective and atom-economical method for the stereoselective assembly of the ring A and B subunits **395** of bryostatins,[131a] as well as the stereoselective preparation of bryostatin analogs.[131b] The key step in these synthetic endeavors was

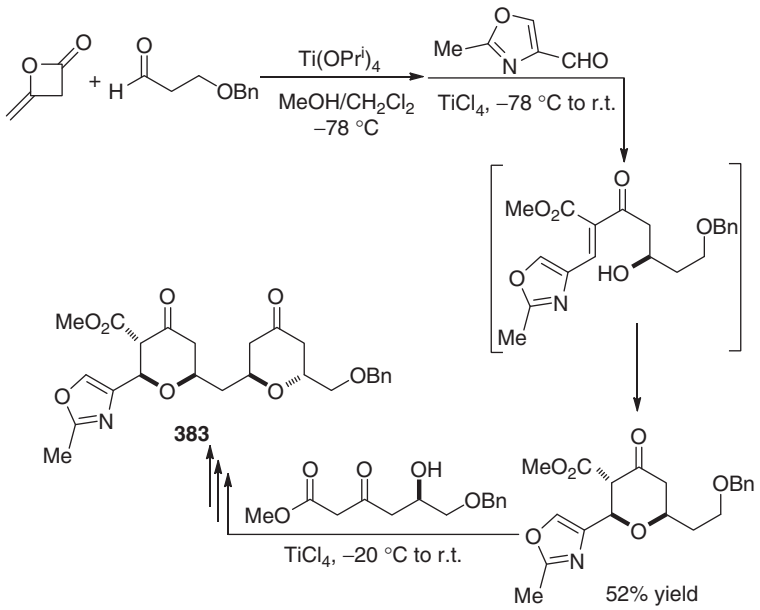


Scheme 92

an Ru-catalyzed tandem alkyne-enone coupling/Michael addition reaction (equation 239 in Scheme 96). The propargylic alcohols and β,γ-enones were then subjected to the optimized coupling/cyclization conditions to afford the geometrically defined exocyclic vinylsilanes **394**, which provided a convenient handle for further functionalization.

Trost and Livingston also demonstrated that the ruthenium complex, along with cocatalysts indium(III) triflate and CSA, can effect the redox isomerization of propargyl alcohols to enals and enones.[132a,b] Based on these studies, the same group found that enones and enals, derived from the [IndRu(PPh_3)$_2$Cl]-catalyzed redox isomerization of primary and secondary propargyl alcohols **396**, underwent an intramolecular oxz-Michael addition sequence to afford tetrahydropyrans **397** and tetrahydrofurans **398** in good yields (equation 240 in Scheme 97).[132c] Unfortunately, efforts to form oxepanes via the isomerization–conjugate addition sequence did not generate the desired cyclic products. Maier and coworkers discovered that metal cations such as Pt(II) or Au(I) were able to promote a formal Meyer–Schuster rearrangement of propargylic alcohols **399**. With a suitably positioned hydroxyl function, a subsequent intramolecular oxa-Michael addition gave 2,5-disubstituted tetrahydrofurans **400** (equation 241 in Scheme 97).[132d]

C-Glycosides have been found to be present in a number of natural products and compounds of pharmaceutical significance. As a consequence, a number of strategies have been developed for the syntheses of *C*-glycosides.[133] *C*-Vinyl glycosides form a unique class of *C*-glycosides that assume importance on account of their unsaturation, which is further amenable to a myriad of chemical reactions. Perumal reported a tandem intramolecular oxa-Michael addition/Wittig reaction sequence for the synthesis of *C*-vinyl furanosides. The 1,2-*O*-isopropylidine group of 5,6-dideoxy-5,6-dehydro-6-nitro-*D*-glucofuranoses **401** was removed with TFA–H_2O, and the anomeric mixture of hemiacetals was heated at reflux with Wittig reagents in acetonitrile to afford the *C*-vinyl glycosides **402** (equation 242 in Scheme 98).[134]



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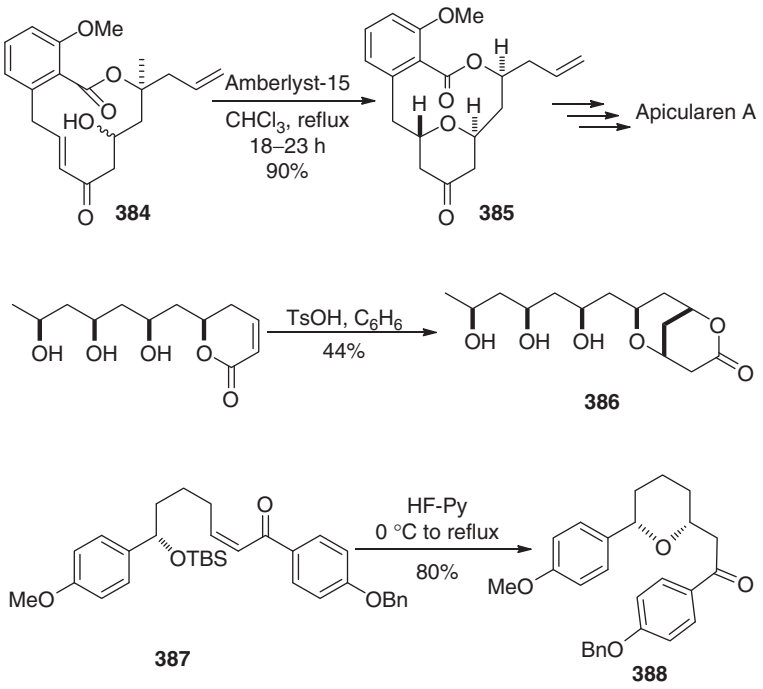
Scheme 93



(232)

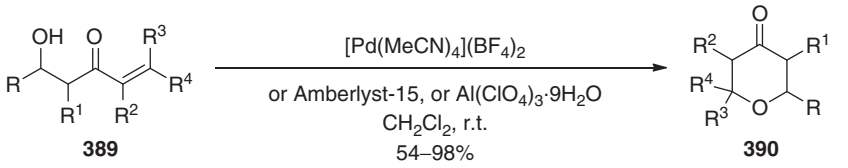
(233)

(234)

Scheme 94

4.01.3 Electron-Deficient Alkynic π-Systems

The addition of stabled nucleophiles (including both carbon and heteroatom nucleophiles) to active alkynes has become a useful method for the formation of carbon–carbon or carbon–heteroatom bond in organic synthesis. This section includes



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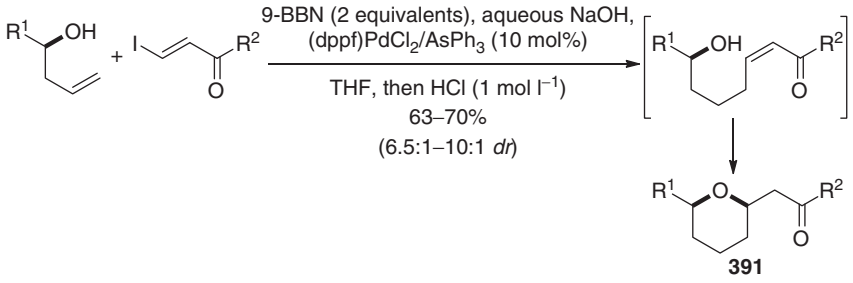

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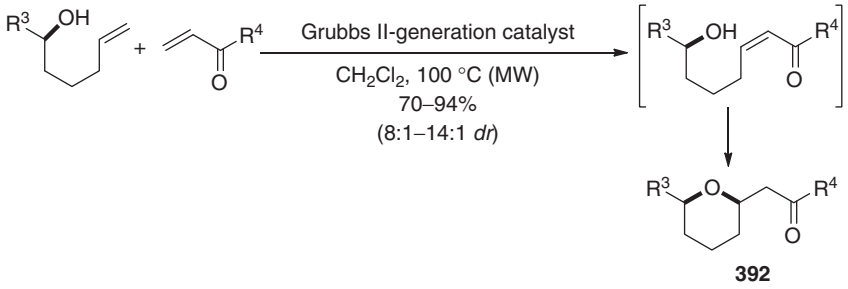

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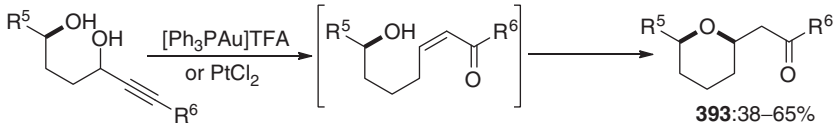

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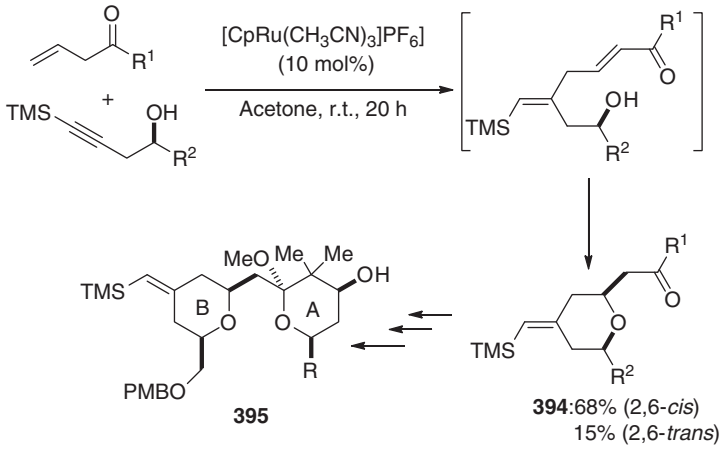
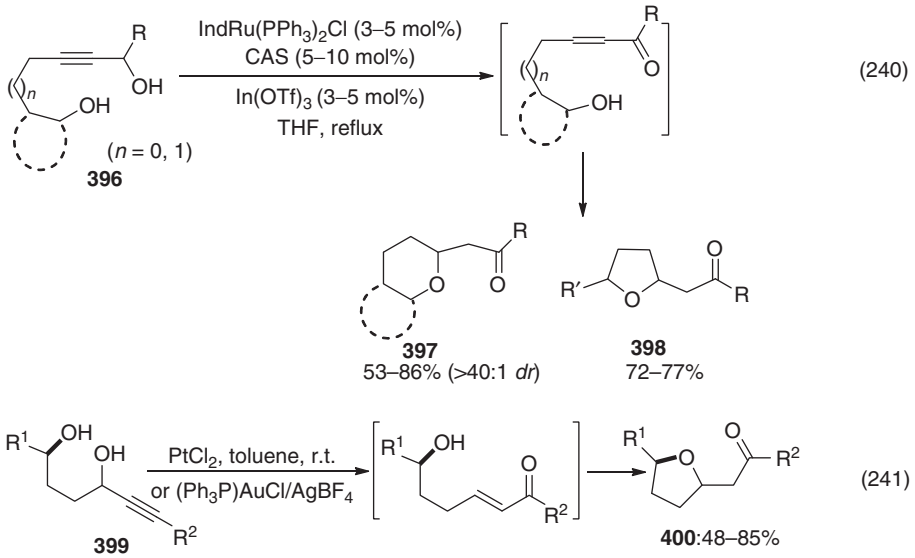
Scheme 95

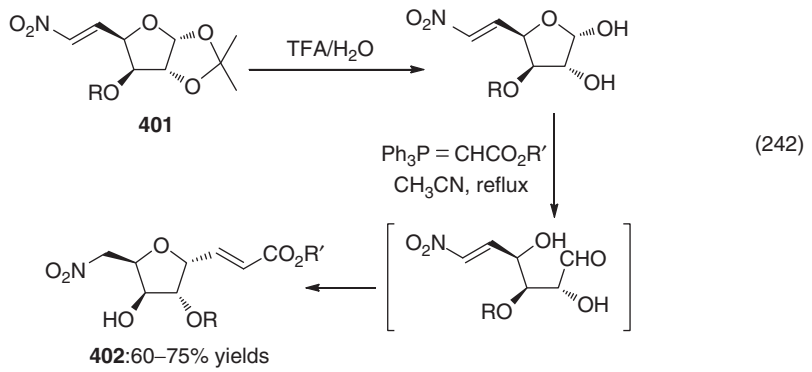


(239)

Scheme 96



Scheme 97

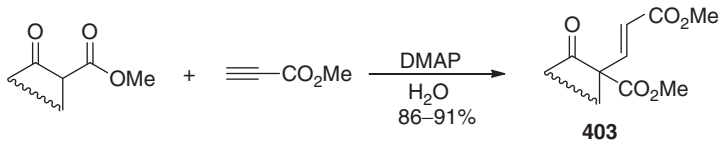


Scheme 98

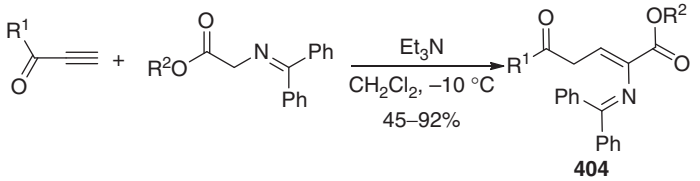
recent advances and some applications of the addition of carbon- and heteroatom nucleophiles to electron-deficient alkynic π-systems.

4.01.3.1 Carbon Nucleophiles

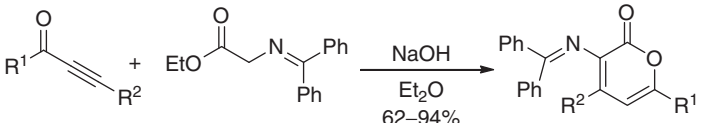
In 1894, Michael had demonstrated that an alkynic ester could also function as the electrophilic component in the conjugate addition by using 1,3-dicarbonyl compounds in the presence of NaOMe.[1c] Over recent decades, many new catalytic systems and different nucleophiles have been found to be used in the addition reactions of electron-deficient alkynes. For example, the Michael addition of active 1,3-dicarbonyl carbon nucleophiles to methyl propiolate under the catalysis of DMAP can produce the corresponding adducts **403** in 86–91% yields in water (equation 243 in Scheme 99).[12b] The addition reaction of *N*-(diphenylmethylene)glycinates to terminal acetylenic ketones in the presence of triethylamine provided an efficient route for the synthesis of α,β-dehydroamino acid derivatives **404** in good yields (equation 244 in Scheme 99),[135a] whereas the internal acetylenic ketones were employed as acceptor substrates in the presence of strong bases, such as NaOH, KOH, and Cs_2CO_3; no α,β-dehydroamino acid derivatives were observed, but 3-amino-2-pyrone derivatives **405** were obtained in good-to-excellent yields (equation 245 in Scheme 99).[135b] In addition, tertiary amines can also trigger a Michael addition to the triple bond of activated alkynes. For example, the reaction of alkyl propiolates with 10-cyan-substituted naphthyridines **406** gave 1-acryloyl-10-cyano-tetrahydrobenzo[*b*] [1,6]naphthyridines **407** as the major products (equation 246 in Scheme 99).[136]



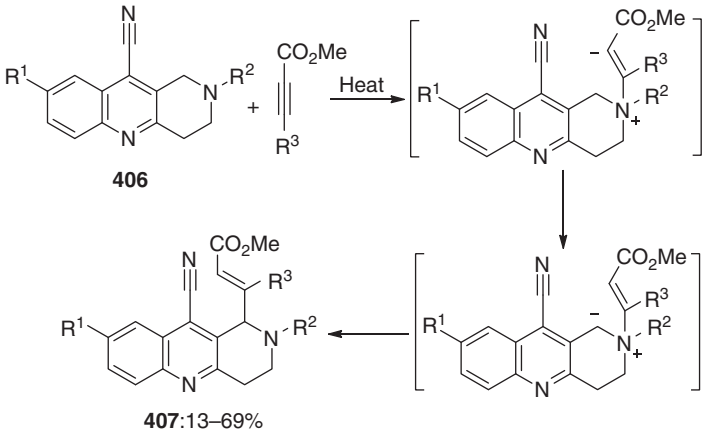
403 (243)



404 (244)



405 (245)



406

407:13–69% (246)

Scheme 99

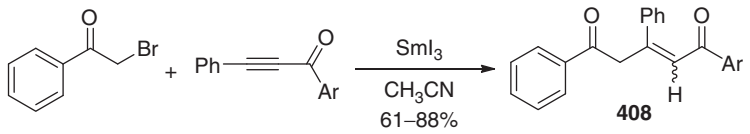
Metal salts or complexes can also be used as catalysts in the Michael reactions of electron-deficient alkynes. Zheng and Zhang showed that in the presence of SmI_3ω-bromo-acetophenone could be converted into a samarium enolate, which underwent the intermolecular Michael addition to α,β-unsaturated alkynones. A series of 1,5-dicarbonyl compounds **408** were obtained in 61–88% yields (equation 247 in Scheme 100).[137] The reaction of aromatic and aliphatic ynones with Me_3SiCN was smoothly catalyzed by $Ni(cod)_2$ in THF, and the corresponding β-cyano enones **409** were obtained in 71–94% yields with low *E*/*Z* selectivities after treatment with AcOH. The predominant formation of the silyloxyallene intermediate was confirmed by ^1H NMR analysis of the reaction mixture. Further reaction of the silyloxyallenes with NBS provides the tetrasubstituted γ-bromo-β-cyano enones **410** in 44–95% yields with excellent *Z*-selectivity ($Z/E > 99/1$) (equation 248 in Scheme 100).[138]

The reaction between a 2-(2-trialkylsilyloxyalkyl)prop-2-enyl (trimethyl)silane and an alk-1-yn-3-one mediated by zinc(II) iodide afforded (*E*)-vinylsilane in moderate yield, which underwent an intramolecular oxy-Michael reaction to provide an efficient synthesis of *cis*-2,6-disubstituted 4-methylenetetrahydropyrans **411**, a key intermediate for synthesis of bryostatins (equation 249 in Scheme 100).[139] The treatment of the furanyl-substituted ynone with 1 mol% of the Echavarren catalyst in dichloromethane at 18 °C led to the formation of the annulated furan **412** in quantitative yield, which is a key intermediate for the synthesis of natural compounds dihydrocrassifolone and crassifolone, respectively (equation 250 in Scheme 100).[140]

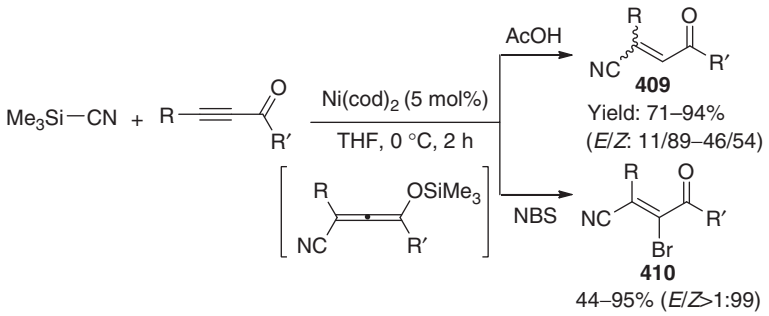
4.01.3.2 Heteronucleophiles

4.01.3.2.1 Nitrogen nucleophiles

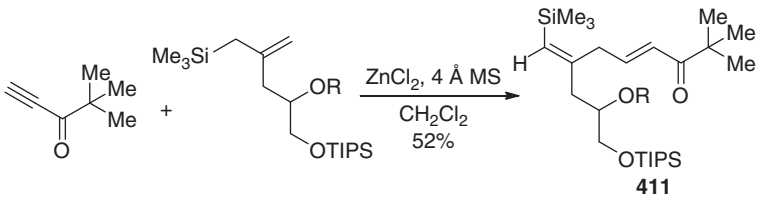
Amines and their derivatives are used as nitrogen nucleophiles in aza-Michael addition to activated alkynes. The aza-Michael addition of amines with alkynone can occur in neat at 80 °C in 98–99% yield, which presented a simple, efficient, and



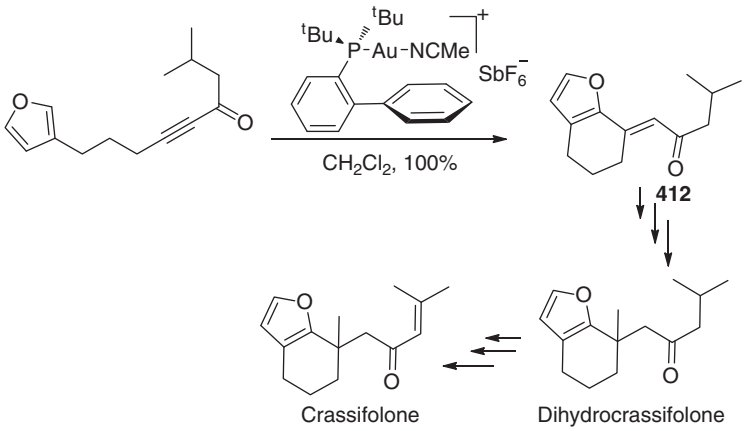
(247)



(248)



(249)

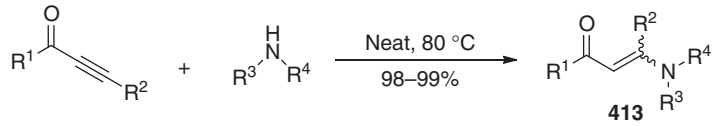


(250)

Scheme 100

environmentally friendly one-pot synthesis of *β*-enaminones **413** (equation 251 in Scheme 101).[141] Aminodiazoacetones, derived from primary amines with bromodiazoacetone, underwent a tandem aza-Michael addition/Wolff rearrangement/nucleophilic ketene cyclization in one pot to give a series of six-membered cyclic enaminones **414** in good-to-excellent yields (equation 252 in Scheme 101).[142] The condensation of (*R*)-(+)-allyl *p*-tolyl sulfoxide with fluorinated nitriles in the presence of $KN(SiMe_3)_2$ at −78 °C gave dienic sulfoxides, which further reacted with alkyl propiolates to generate fluorinated 1,4-dihydropyridines **415** via an intermolecular aza-Michael addition and intramolecular Michael addition (equation 253 in Scheme 101).[143]

Hydrazones can also be employed as nitrogen nucleophilies in the aza-Michael addition of activated alkynes. Shi and co-workers demonstrated that the reaction of a series of hydrazones with diethyl acetylenedicarboxylate proceeded well in the presence of organic bases, such as DMAP, DBU, and DABCO (equation 254 in Scheme 102).[144] Interestingly, the reaction of 1,2-diaminoethane with diaryl ketoalkynes in the high temperature led to the full scission of the triple bond. Acetophenone and imidazoline fragments were obtained as main products (equation 255 in Scheme 102).[145]



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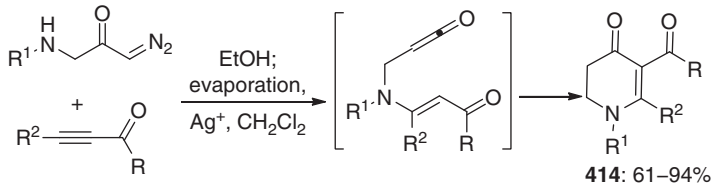
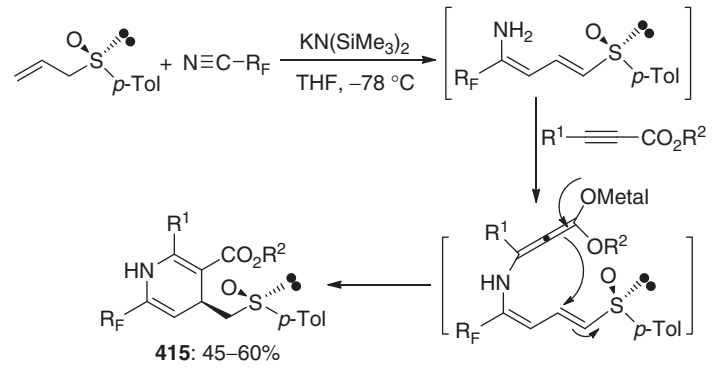
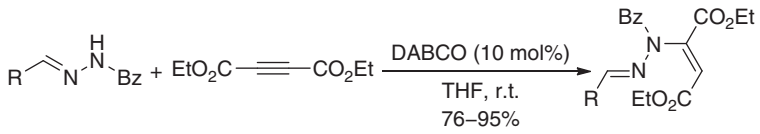


(252)

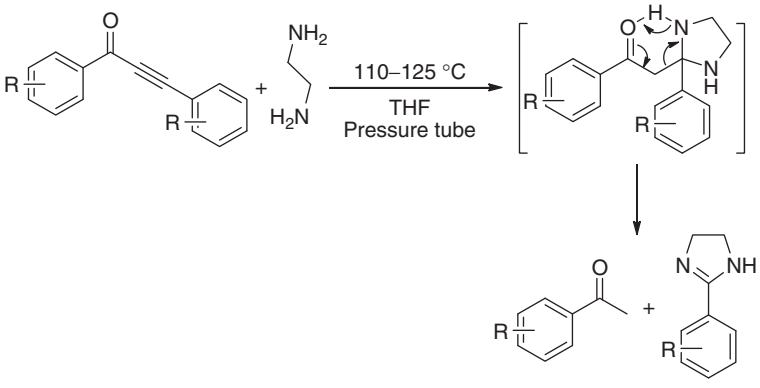


(253)

Scheme 101

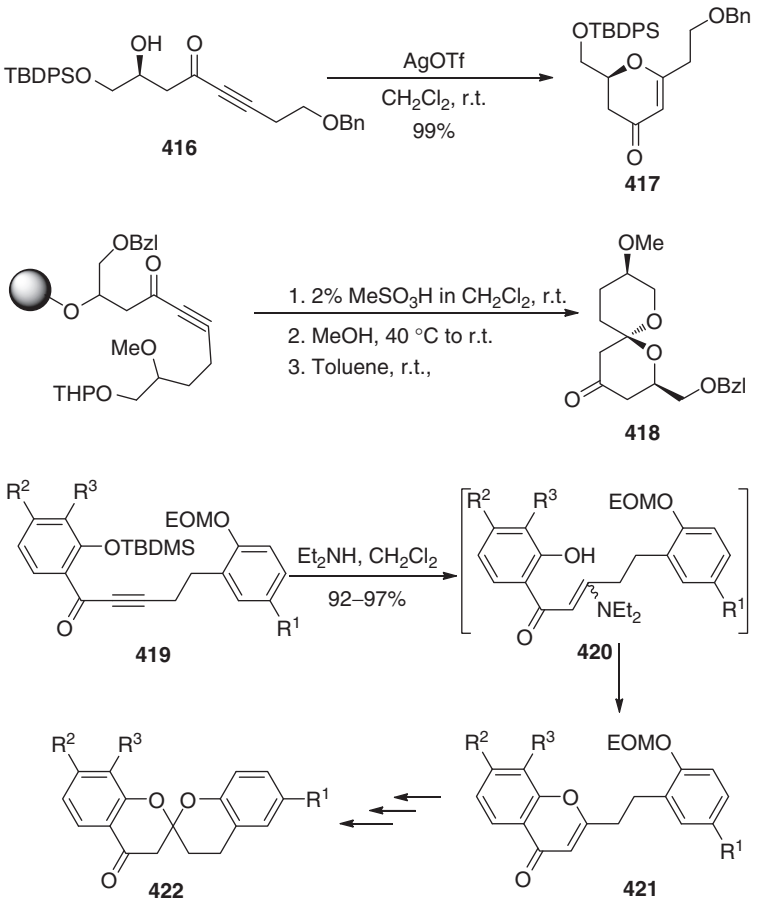


(254)



(255)

Scheme 102

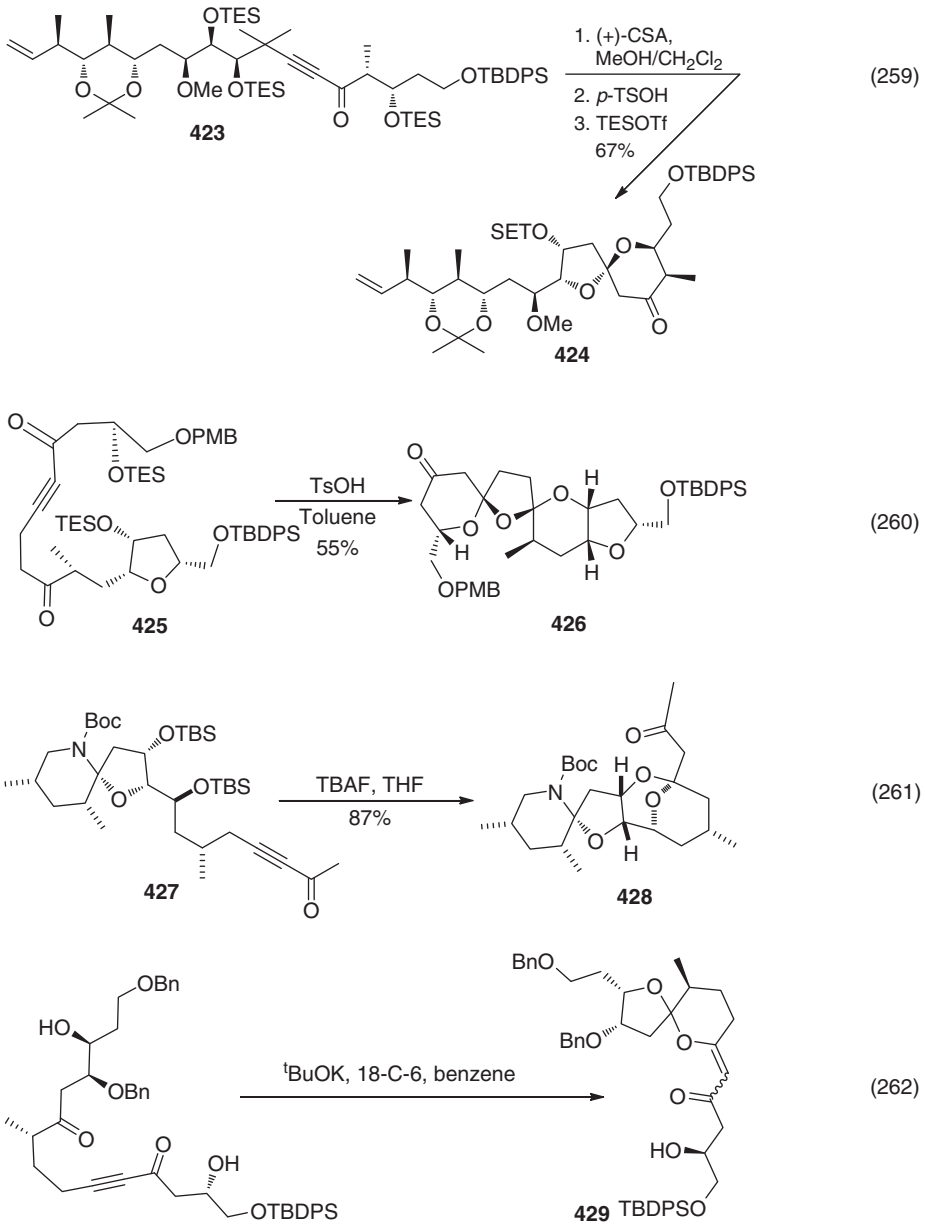


Scheme 103

4.01.3.2.2 Oxygen nucleophiles

The Michael addition of oxygen nucleophiles to active alkynes is very useful for the construction of hydropyran or furan moiety in natural products. An intramolecular oxa-Michael addition of *β*-hydroxyynone **416** gave 5,6-dihydropyranone **417**, which was a key intermediate in the synthesis of the tetrahydropyran subunit (C8–C20 fragment) of (−)-dactylolide and (−)-zampanolide (equation 256 in Scheme 103).[146a] The same strategy was also used in the constructing ring system of maitotoxin.[146b] A double intramolecular oxa-Michael reaction was the key step for the synthesis of spiro[5.5]ketals **418**, which was the core structure of numerous biologically active natural products (equation 257 in Scheme 103).[147a] The treatment of ynone **419** dichloromethane solutions with diethylamine led to the deprotection of the TBDMS group with concomitant formation of the isolable enaminoketone intermediate **420**. Intramolecular 6-*endo-dig* cyclization of this intermediate yielded the desired benzopyrone **421** via an addition–elimination sequence. This method was used in the synthesis of 6,6-bisbenzannulated spiroketals **422** related to the rubromycins (equation 258 in Scheme 103).[147b]

A double intramolecular oxa-Michael addition of ynone **423** furnished spiro[4.5]ketal **424** in 67% yield in the presence of (+)-CAS in methanol-dichloromethane, followed by *p*-TsOH. The spiro[4.5]ketal was the important intermediate for the total synthesis of calyculin C (equation 259 in Scheme 104).[148] The treatment of ynedione **425** with *p*-TsOH·H_2O in toluene at room temperature for 1–2 days led to the selective cleavage of the Si–O bonds of TES ethers in ynedione, followed by subsequent double oxa-Michael addition producing trioxadispiroketal **426**, which was the key moiety of azaspiracid-1 (equation 260 in Scheme 104).[149a] Treatment of ynone **427** with TBAF in THF at room temperature promoted silyl ether cleavage, and double oxa-Michael addition of the liberated oxygen atoms provided the fully functionalized 2,9-dioxabicyclo[3.3.1]nonane **428**, as the key ring system of the azaspiracid natural products (equation 261 in Scheme 104).[149b] In the basic condition, the intramolecular addition of diol to ynone gave spiro[4.5]ketal **429**, which was further transformed into the natural compound of spirastrellolide A (equation 262 in Scheme 104).[149c]

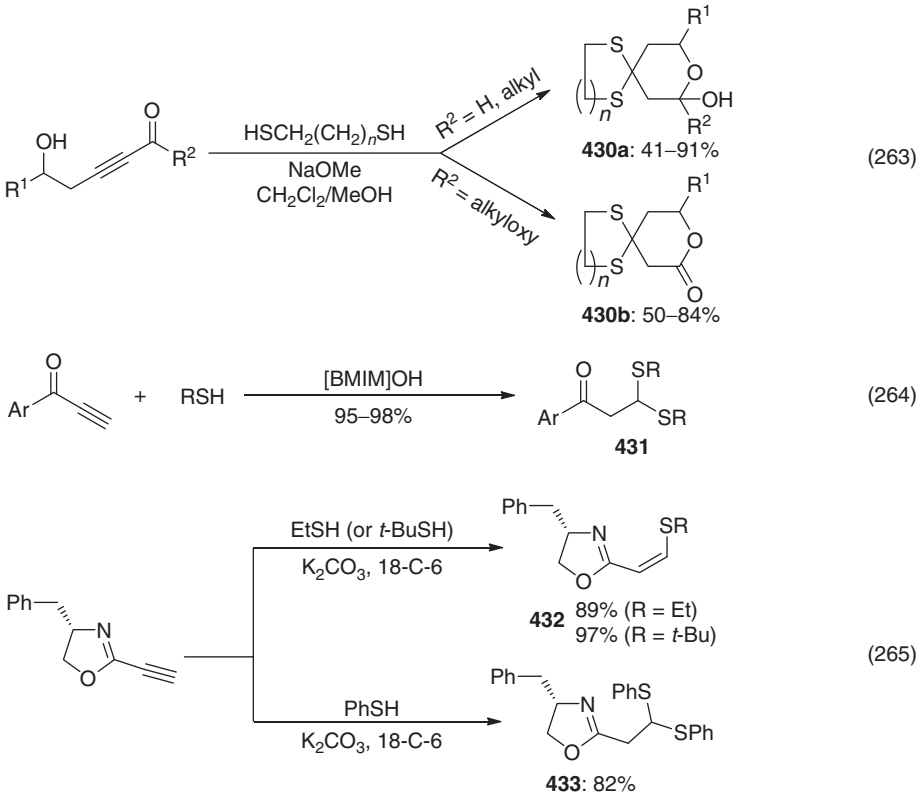


Scheme 104

4.01.3.2.3 Sulfur nucleophiles

Ethane and propane dithiol can be added conjugatively to ynones, ynals, terminal ynoates, and bisynones to give various protected 1,3-dicarbonyl compounds under the catalysis of NaOR, MgO, etc.[150] For example, the double conjugate additions of ethane and propane dithiols to a wide variety of propargylic carbonyl compounds took place efficiently in the presence of sodium methoxide, followed by tandem *in situ* cyclization leading to tetrahydropyran derivatives **430** (equation 263 in Scheme 105).[150a–c] Furthermore, the treatment of thiols to α,β-acetylenic ketones in basic ionic liquid [BMIM]OH also underwent the double conjugate addition producing β-keto 1,3-dithio-derivatives **431** in excellent yields (equation 264 in Scheme 105).[150e] In addition, molecular sieve and dimethyl sulfoxide also promoted some double-Michael addition between dithiols and acetylenic carbonyl compounds.[151]

The similar double-Michael addition occurred when alkynyl oxazoles were used as starting materials. Using ethanethiol and the sterically hindered *t*-butyl thiol, the addition to 2-ethynyl-4-benzyloxazoline afforded the corresponding *Z*-form adducts **432** in good-to-excellent yields. Interestingly, in similar conditions thiophenol gave the dithioacetal **433** (equation 265 in Scheme 105).[152]



Scheme 105

Disulfides could be activated by samarium diiodide, and underwent the Michael addition into the conjugated alkynones to give *Z*-product **434** favorably in low temperature. Furthermore, the tandem Michael/aldol sequence took place smoothly using three components of diorganyl disulfides, conjugated alkynones, and carbonyl compounds to afford the desired products **435** in 82–96% yields (equation 266 in Scheme 106). A similar reaction also occurred when disulfides were displaced by diselenides.[153]

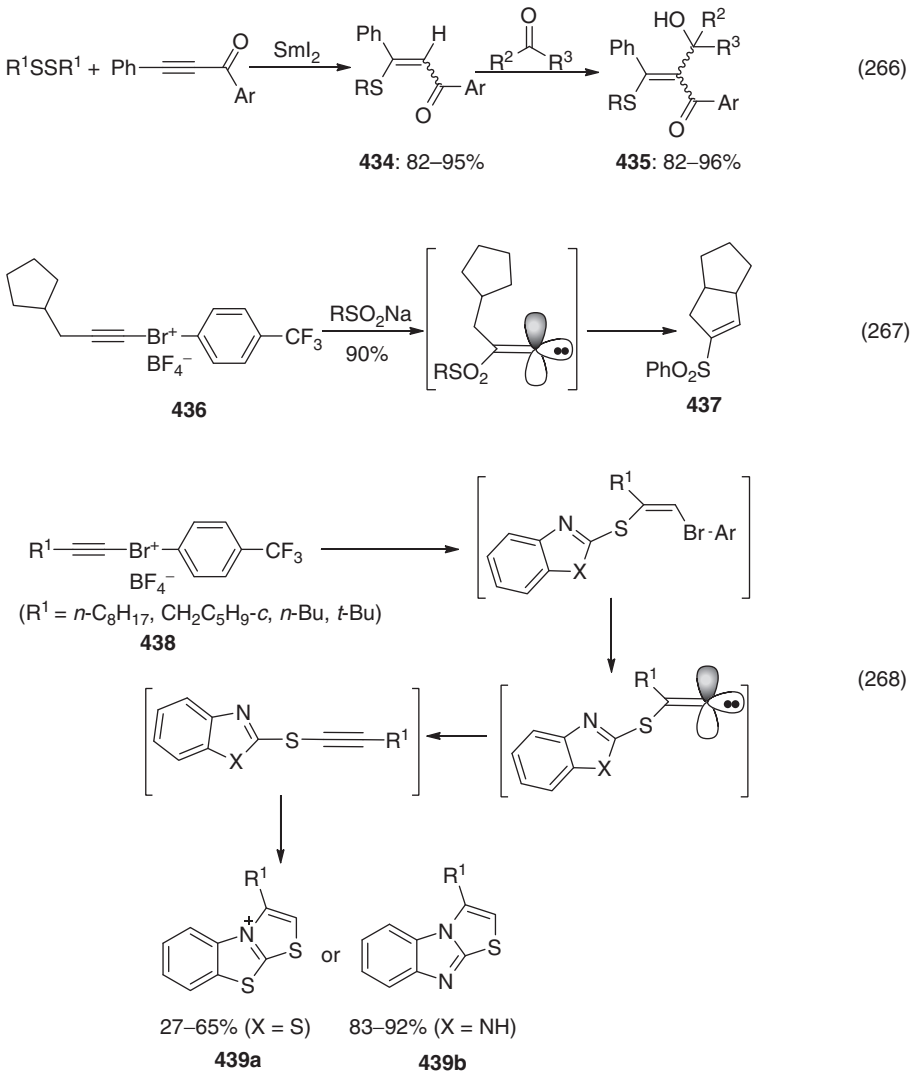
Alkynylbromanes can also act as Michael acceptors. Treatment of 1-alkynyl[*p*-(trifluoromethyl)phenyl](tetrafluoroborato)-λ^3-bromanes **436** with sodium benzenesulfinate or sodium trifluoromethanesulfinate in dichloromethane under argon led to the formation of 1-sulfonylcyclopentenes **437** via a tandem Michael/carbene insertion reaction (equation 267 in Scheme 106).[154a] When 1-alkynyl [*p*-(trifluoromethyl)phenyl](tetrafluoroborato)-λ^3-bromanes **438** were treated with 2-mercapto-benzimidazole or benzothiazole in dichloromethane at 0 °C under argon, tricyclic heterocycles **439** were obtained in high yields via a domino Michael addition/carbene rearrangement/cyclization sequence (equation 268 in Scheme 106), whereas the treatment with 2-mercapto-benzoxazole only afforded 1-alkynyl sulfides.[154b]

4.01.3.2.4 Other nucleophiles

Other heteroatom nucleophiles include phosphor, halogen, selenium, tellurollium, etc. Several earlier references involving the phospha-Michael addition to alkynic acceptors were summarized in the review by Enders and coworkers.[118f] Recently, Oshima and coworkers demonstrated that treatment of 1-alkynyldiphenylphosphines with diphenylphosphine afforded (*Z*)-1,2-bis(diphenylphosphino)-1-alkenes **440** in the presence of catalytic amounts of copper(I) iodide and cesium carbonate in DMF at 20 °C (equation 269 in Scheme 107).[155]

The Michael-type addition of HF to 1-alkynyl(phenyl) iodonium tetrafluoroborates afforded (*Z*)-2-Fluoro-1-alkenyl(phenyl) iodonium tetrafluoroborates **441** stereoselectively in moderate-to-good yields (equation 270 in Scheme 107).[156] (*Z*)-2-Fluoro-1-alkenyl-(phenyl)-iodonium tetrafluoroborates could be converted into fluorine-containing α,β-unsatuarated ester **442** under the catalysis of $PdCl_2$ in the presence of CO and methanol. Halogen addition products were obtained from electron-deficient alkynes **443** in good yields via chalcogenide-Lewis acid-mediated reactions (equation 271 in Scheme 107).[157]

The Michael addition of alkyl or aryl tellurolate anion into activated alkynes proceeded well with subsequent trapping of a vinyl anion in the presence of electrophiles (aldehydes and ketones) (equation 272 in Scheme 107).[158] The corresponding products **444** can be further transmetalated to lithium, copper, or zinc complexes for the construction of tri- or tetrasubstituted alkenes.



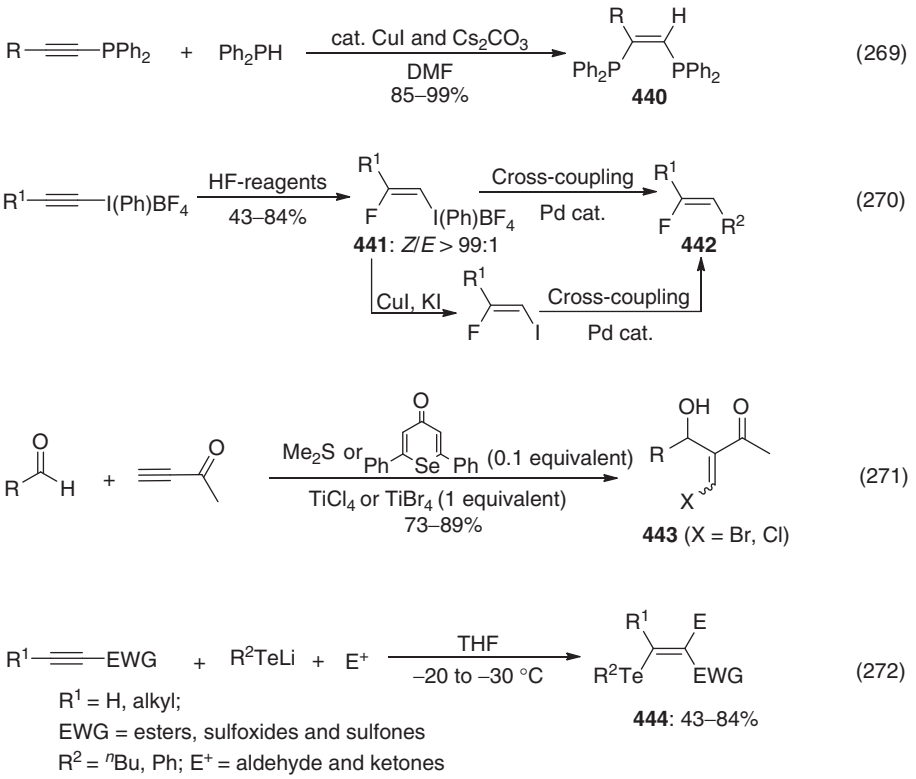
Scheme 106

4.01.4 Electron-Deficient Allenic π-Systems

Several impressive reviews have involved the nucleophilic additions to electron-deficient allenes.[159] This section will briefly highlight recent advances in inter- and intramolecular nuclueophilic additions of 2,3-allenoic acids, 2,3-allenoates, and 1,2-allenyl ketones.

4.01.4.1 Intermolecular Nucleophilic Addition

Allenoates are an attractive substrate class for Lewis base catalysis due to their diverse reactivity. Addition of a Lewis base to the electrophilic, sp-hybridized β-carbon of α-allenic esters results in the generation of a zwitterionic enolate-like intermediate. The reactivities of the α- and γ-carbons of the carbonyl group in the zwitterion are different: the α-carbon is nucleophilic, whereas the γ-carbon is electrophilic. In 1995, Zhang and Lu reported an umpolung addition of oxygen and carbon nucleophiles to the terminal allenoates under the catalysis of a phosphine. A series of inverse addition products **445** and **446** were regioselectively obtained in good yields (equations 273 and 274 in Scheme 108).[160a] Later, the same group developed a phosphine-catalyzed tandem umpolung addition and intramolecular conjugate addition sequence. Reaction of 1,3-dicarbonyl compounds with ethyl 2,3-allenoate and 1,2-allenyl ketones afforded dihydrofuran derivatives **447** with good yields (equation 275 in Scheme 108).[160b]

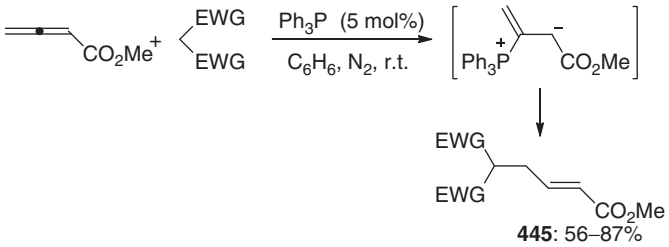


Scheme 107

Starting from 1,2-allenic ketones **448** with diethyl malonate, Ma's group developed an efficient methodology for the synthesis of polyfunctionalized *β,γ*-unsaturated ketones **449** in 2002 (equation 276 in Scheme 108).[160c] The reaction shows good 1,4-regio- and *E*-stereoselectivity. These adducts can undergo carbon double bond migration and lactonization reaction promoted by K_2CO_3. Using this approach, they presented a convenient route for *α*-pyrone derivatives **450** from 1,2-allenic ketones **448** and diethyl malonate catalyzed by K_2CO_3 in one pot via a sequential Michael addition carbon–carbon double bond migration–lactonization process (equation 277 in Scheme 108).[160d] In 2005, the same group developed a simple and efficient procedure for the highly stereoselective preparation of *β*-indolyl *α,β*-unsaturated (*E*)-enones **451** from indoles and 1,2-allenic ketones, through the highly stereoselective (*E*)-hydroindolylation reactions of the *β,γ*-C=C bond of 1,2-allenic ketones in the presence of 5 mol% $Sc(OTf)_3$. In the same condition, double indolylation of 1,2-allenic ketones afforded *β,β*-bisindolyl ketones **452** in good yields (equation 277 in Scheme 108).[160e]

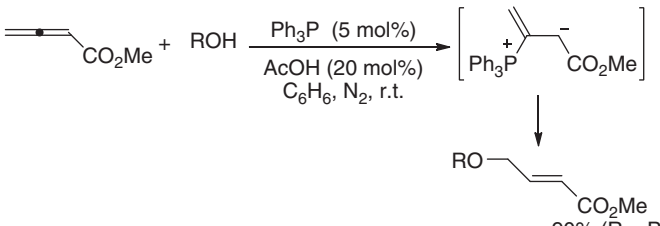
More recently, Jia and coworkers found that isocyanide-triggered nucleophilic addition toward allenoate would essentially lead to the generation of a zwitterionic intermediate, which could experience further cyclization to form five-membered carbocycles when electron-deficient olefins were used as trapping agent. Using this protocol, they presented an efficient and atom-economical way to synthesize highly functionalized five-membered carbocycles **453** with exclusive regioselectivity and stereoselectivity in high yields (equation 278 in Scheme 109).[161a] Furthermore, they developed an efficient way to construct spirocyclic oxindoles-butenolide derivatives **454** in up to 91% yield by using three-component reactions from isocyanides, allenoates, and isatins (equation 279 in Scheme 109).[161b,c] Replacing isatins with isatylidene malonotriles, the same group described another multi-component reaction to efficiently generate functionalized spirocyclic oxindoles **455**. They found that the behavior of allenoate has been greatly changed in the presence of water, which leads to an unprecedent four-component cycloaddition to produce highly unusual tricyclic oxindole products **456** through an efficient triple Michael/cyclization process (equation 280 in Scheme 109).[161d] This protocol provides a new opportunity to synthesize natural product-like spirocyclo oxindole molecules.

Based on Lu's seminal investigations, Liu and coworkers presented an annulation of thiamides with ethyl 2,3-allenoate under the catalysis of triphenylphosphine to afford the adducts **457** (equation 281 in Scheme 110),[162a] whereas Miller's group demonstrated that allenoate esters could be condensed with 2-amino thiazoles to deliver pyrimidones **458** of various structures (equation 282 in Scheme 110).[162b] One year later, Virieux et al. described an triphenylphosphine-catalyzed umpolung addition of electron-deficient allenes with azoles **459**, such as imidazole, pyrrazole, triazole, phthalimide, and their benzoanalogs. Furthermore, this methodology was also extended to the addition/cyclization reaction between electron-deficient allenes and pyrrole-2-carboxaldehyde to give indolizine **460** in the presence of catalytic amounts of tributylphosphine (equations 283 and 284 in Scheme 110).[162c]



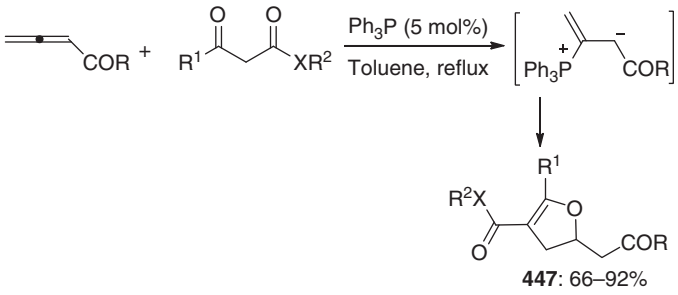
445: 56–87%

(273)



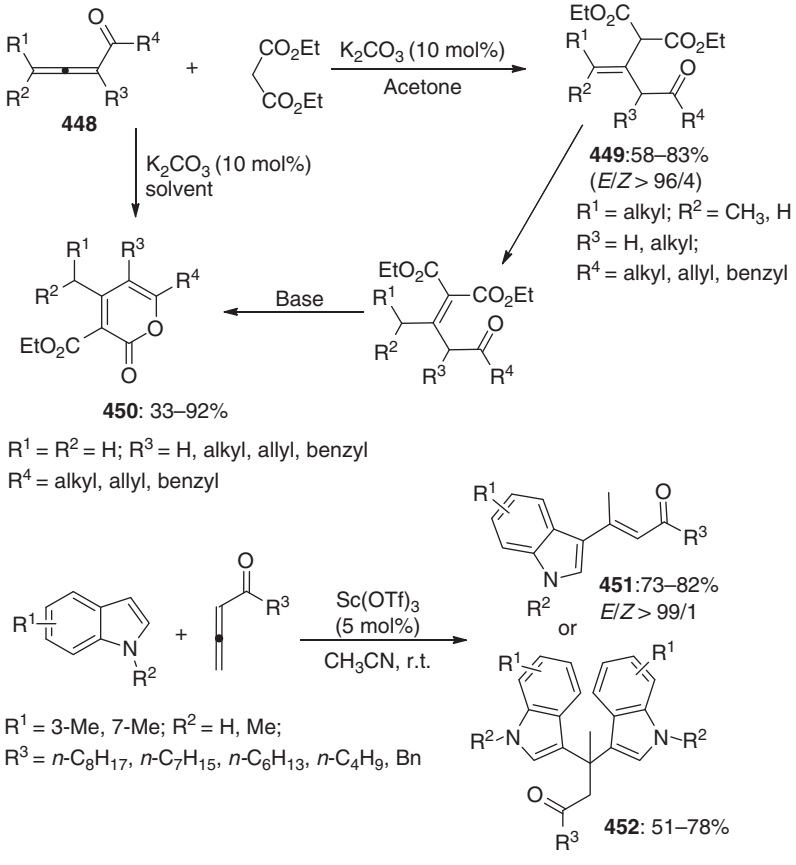
446 90% (R = $PhCH_2$)
60% (R = Me)

(274)



447: 66–92%

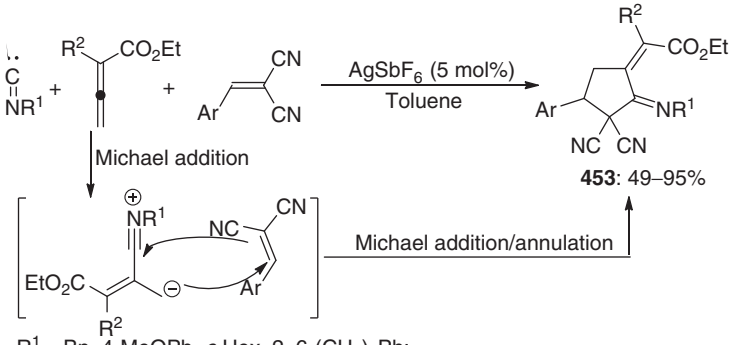
(275)



(276)

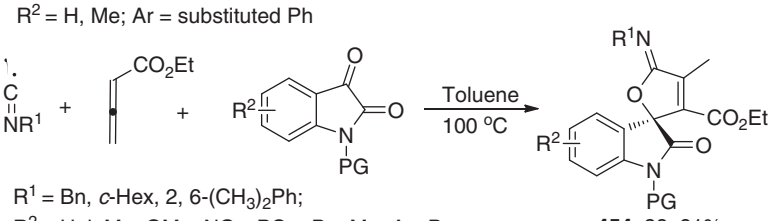
(277)

Scheme 108



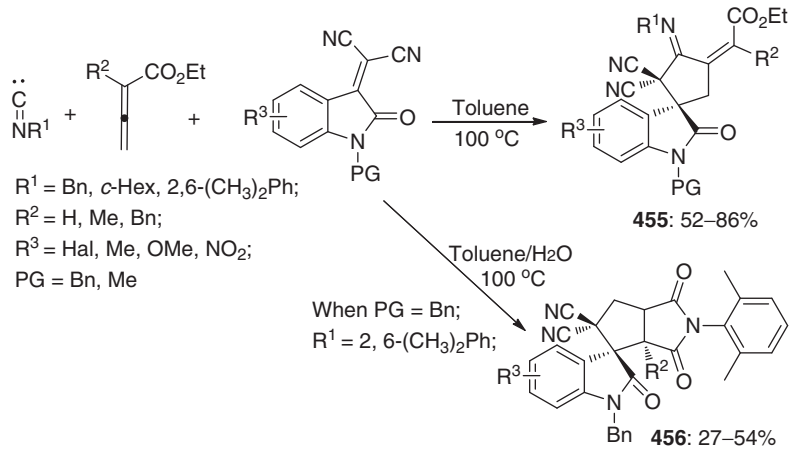
(278)

R^1 = Bn, 4-MeOPh, *c*-Hex, 2, 6-$(CH_3)_2$Ph;
R^2 = H, Me; Ar = substituted Ph



(279)

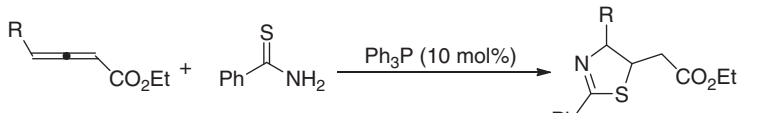
R^1 = Bn, *c*-Hex, 2, 6-$(CH_3)_2$Ph;
R^2 = Hal, Me, OMe, NO_2; PG = Bn, Me, Ac, Boc



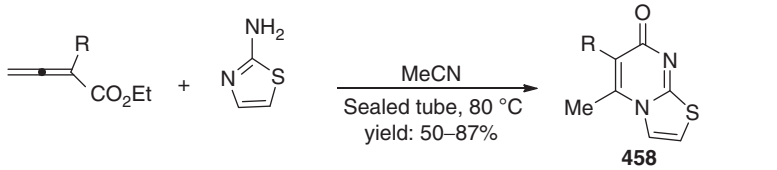
(280)

R^1 = Bn, *c*-Hex, 2,6-$(CH_3)_2$Ph;
R^2 = H, Me, Bn;
R^3 = Hal, Me, OMe, NO_2;
PG = Bn, Me

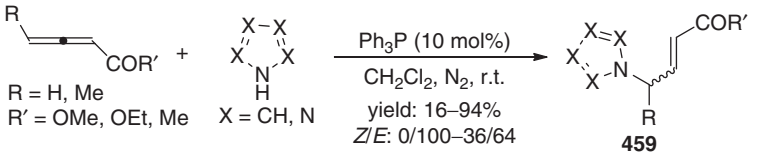
Scheme 109



(281)

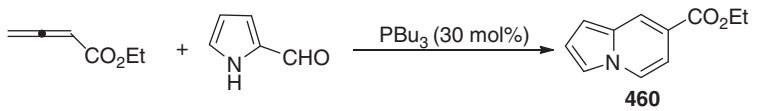


(282)



(283)

R = H, Me
R′ = OMe, OEt, Me
X = CH, N



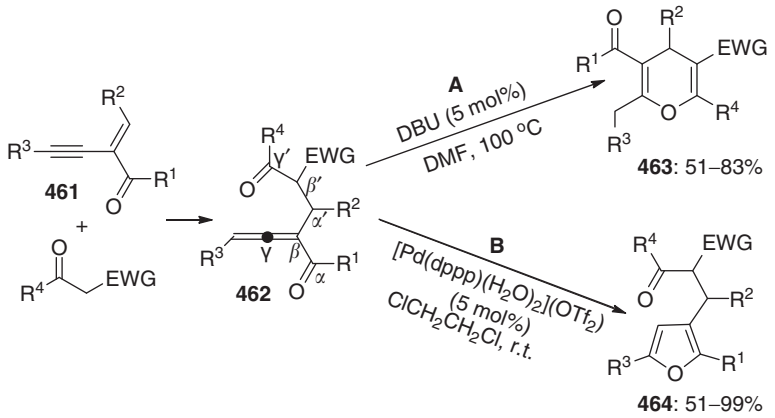
(284)

Scheme 110

4.01.4.2 Intramolecular Nucleophilic Addition

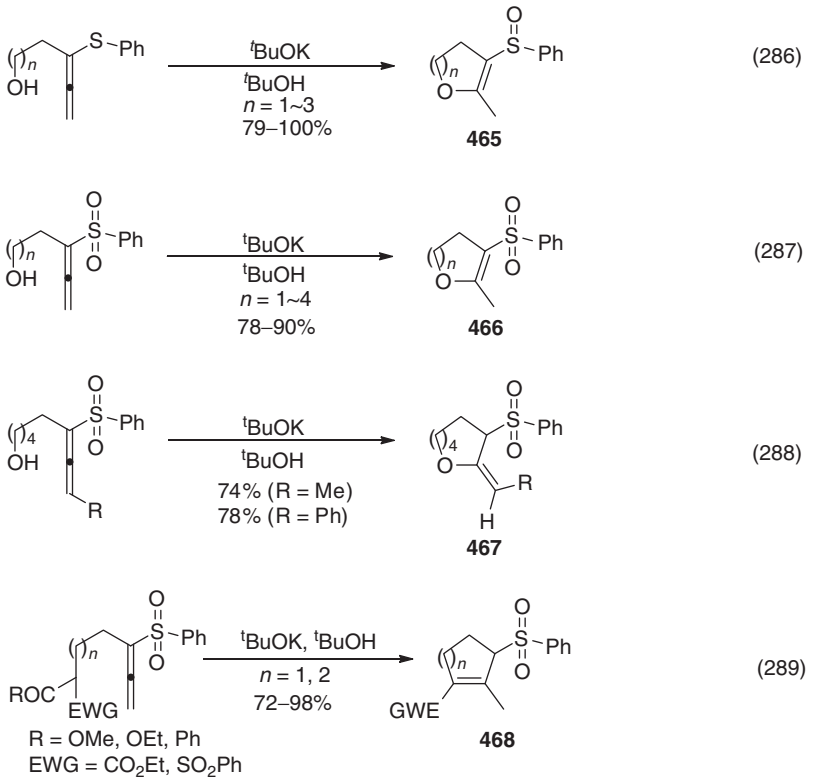
Recently, Xiao and Zhang reported a catalyst-controlled regiodivergent tandem Michael addition/cyclization for the synthesis of 4*H*-pyrans and furans from the same 1,2-allenyl ketone intermediates.[163] The DBU-catalyzed reaction of 1-(1-alkynyl)- 2-alken-1-ones **461** with 1,3-dicarbonyl compounds produced 4*H*-pyrans in moderate-to-excellent yield, whereas the cationic Pd(II)-catalyzed reaction afforded furans regioselectively (equation 285 in Scheme 111). The intermolecular Michael addition of 1,3-dicarbonyl compounds to 2-(1-alkynyl)-2-alken-1-ones gave intermediate allenyl ketones **462**. Two kinds of C–O bond formation patterns then occurred via the interaction of the allenyl group with two different carbonyl groups (α carbonyl and γ' carbonyl group) leading to functionalized 4*H*-pyrans **463** (Path A) or furans **464** (Path B).

Mukai and coworkers found that treatment of the terminal allenyl sulfoxides and sulfones possessing a proper α-hydroxy appendage at the C-1 position with potassium *tert*-butoxide afforded the five- to eight-membered oxacycles (**465** and **466**, equations 286 and 287 in Scheme 112).[164a] This ring closure could be rationalized in terms of the *endo*-mode Michael-type



(285)

Scheme 111



(286)

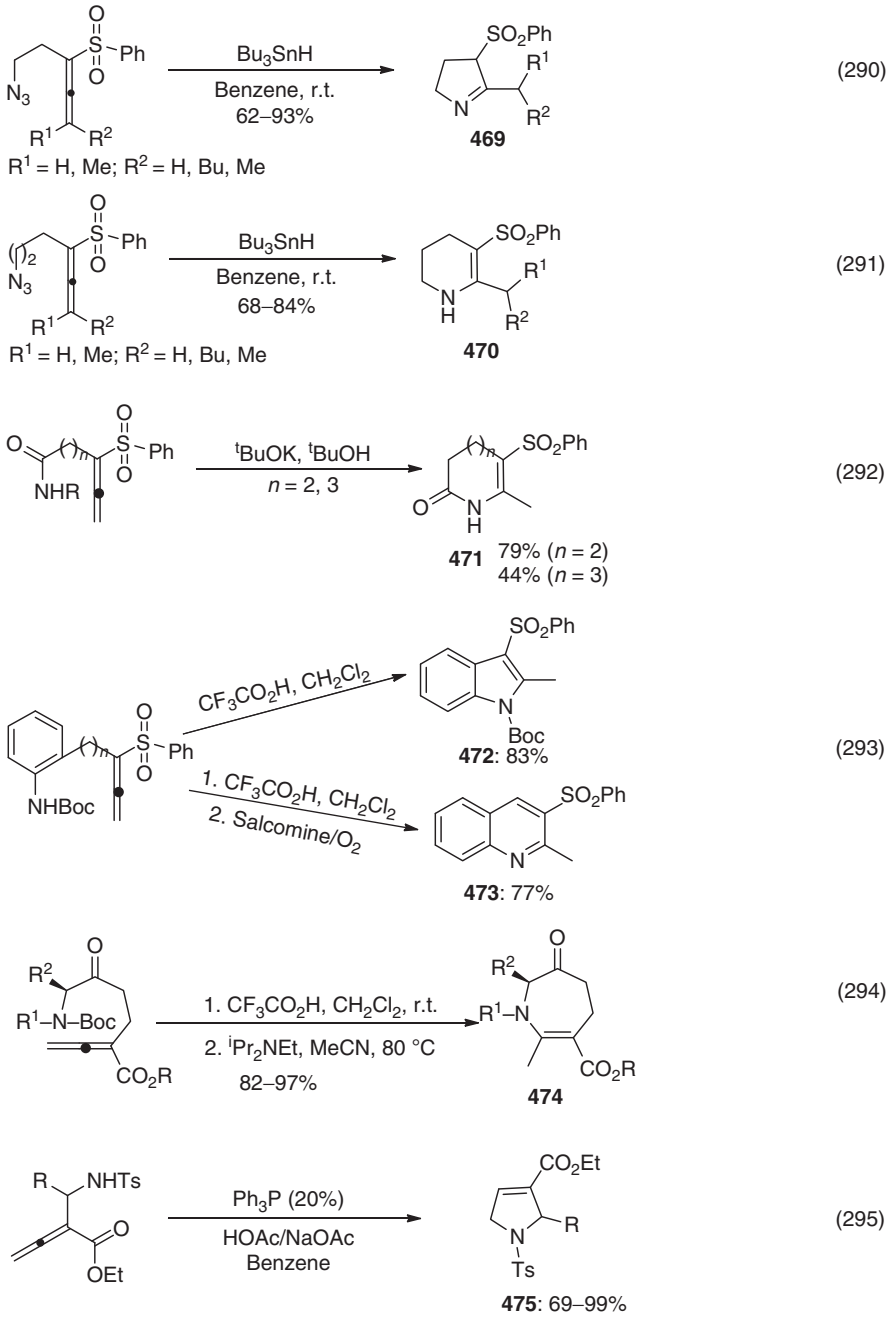
(287)

(288)

(289)

Scheme 112

reaction initiated by the attack of the terminal hydroxy anion at the electron-deficient sp-hybridized carbon of the allenyl functionality, followed by double bond migration. It is noteworthy that two internal allenyl sulfones were reacted under standard basic conditions at room temperature, giving rise to the easy *endo*-mode cyclization as expected and producing oxocanes **467** with the (*E*)-ethylidene moiety (equation 288 in Scheme 112). In addition, the intramolecular ring-closure reaction of the allenyl sulfones with suitable internal carbon nucleophiles in an *endo*-mode manner afforded the adducts, accompanied by dealkoxycarbonylation or debenzoylation to give the 1,2,3-trisubstituted cyclopentene and cyclohexene derivatives **468** (equation 289 in Scheme 112).[164b] A similar procedure for constructing monocyclic five-, six-, and seven-membered azacycles **469–471** as well as azabicyclo[*m.n.*0] compounds **472–474**, through the *endo*-mode ring-closing reaction of allenylazido and allenylamido derivatives under neutral conditions, was also developed by Mukai et al. (equations 290–293 in Scheme 113)[164c] and Miller et al.[162b] (equation 294 in Scheme 113). Recently, Kwon and coworkers demonstrated that the conversion of 2,3-allenamides to 3-carbethoxy-2-alkyl-3-pyrrolines **475** can also be facilitated through Ph_3P-catalyzed intramolecular γ-umpolung addition (equation 295 in Scheme 113).[164d]



Scheme 113

4.01.5 Conclusion

The addition of stabilized nucleophiles to electron-deficient π-systems has been a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds in organic synthesis. This chapter has provided an up-to-date overview of recent advances in this area. One can foresee that many more novel addition reactions and applications involving electron-deficient alkenes, alkynes, and allenes will be developed in the future.

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4.02 Nucleophilic Addition-Electrophilic Coupling with a Carbanion Intermediate

X Song, University of New Mexico, Albuquerque, NM, USA, and Zhengzhou University, Zhengzhou, China
W Wang, University of New Mexico, Albuquerque, NM, USA, and East China University of Science & Technology, Shanghai, China

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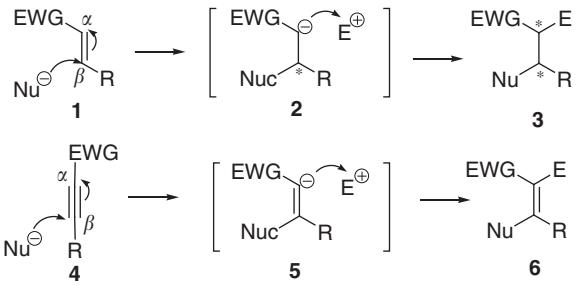
Glossary

Alkenals and enals Unsaturated chemical compounds or functional groups consisting of a conjugated system of an alkene and an aldehyde.
Alkynals and ynals Unsaturated chemical compounds or functional groups consisting of a conjugated system of an alkyne and an aldehyde.
Allenamines One end 'C' atom is replaced by 'N' atom in an allene.
Cascade (or domino or tandem) reaction A consecutive series of organic reactions proceed in 'one-pot' without isolation of reaction intermediates.
Enamine catalysis Forming catalytic quantities of an active enamine nucleophile.
Enones Unsaturated chemical compounds or functional groups consisting of a conjugated system of an alkene and a ketone.
Iminium catalysis Forming catalytic quantities of an activated iminium electrophile.
Star polymer Several linear polymer chains connected at one point.

4.02.1 Introduction

The strategy of nucleophilic addition-electrophilic coupling has been widely explored in modern organic synthesis. The cascade (or domino, or tandem) process, in which at least two bond-forming steps take place in a single operation, enables a rapid increase in molecular complexity from readily available starting materials. The approach can dramatically improve the synthetic efficiency in a fashion of the atom economy, and it naturally falls into the category of a cascade reaction.[1,2]

In a nucleophilic addition-electrophilic coupling process, the substrate **1** or **4** generally contains a polarized C–C π-bond (Scheme 1). The electronic withdrawing group (EWG) influences the pattern of the electronic density of the π-bond, and thus renders the β-carbon more electrophilic. Furthermore, it also provides a site for interaction with a catalyst for facilitating the cascade transformation and stereoselective manipulation. The nucleophile and electrophile can be either discrete or integrated in one single compound in a 2- or 3-component reaction.



Scheme 1 Basic strategies of nucleophilic addition-electrophilic coupling. EWG = electronic withdrawing group; Nu = nucleophile; E = electrophile; R = alkyl or aryl group; * = stereogenic center.

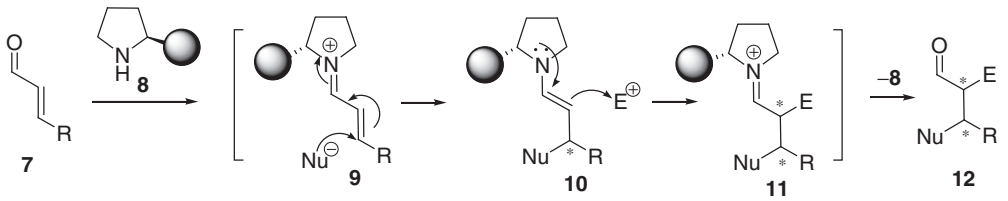
The broad potential selection of α,β-unsaturated compounds, together with a broad array of Michael donors and carbophilic electrophiles renders the strategy of nucleophilic addition-electrophilic coupling one of the central tenets and instruments in the arsenal of modern organic synthesis. The cascade is initiated by a Michael addition (or conjugated addition, or 1,4-addition) of a nucleophile. The substrates are usually α,β-unsaturated carbonyls and nitroolefins (**1**), or acetylenic carbonyl compounds (**4**). The Michael addition leads to a new nucleophilic species, which can further engage in a subsequent electrophilic coupling with a new electrophile. The integration of a conjugate addition-triggered cascade transformation with trappings of carbophilic electrophiles is the major focus of this chapter, which is categorized based on the types of Michael acceptors used in nucleophilic addition-electrophilic couplings.

4.02.2 α,β-Unsaturated Aldehydes

Although α,β-unsaturated aldehydes nowadays serve as one of the most versatile templates for nucleophilic addition-electrophilic coupling cascade processes, they had been less widely used compared with analogous enones before organocatalysis.[3] The reason

attributes to the aldehyde functionality are more readily subject to 1,2-nucleophilic addition than 1,4-conjugated addition when an organometallic catalyst is used.

The pioneering work on iminium catalysis by MacMillan and coworkers offers an effective approach to the conjugate addition of enals (Scheme 2).[4] Reaction of an enal **7** with chiral amine **8** produces an iminium ion **9**, which renders the β-carbon activated for a nucleophilic attack. The exclusive 1,4-addition arises from the steric hindrance imposed by the bulky catalyst **8** covalent bonded iminium ion **9**, which efficiently blocks 1,2-addition. The activation mode has been widely and successfully explored in Michael addition reactions in high yields and with high enantioselectivities generally observed.[5]



Scheme 2 α,β-Unsaturated aldehydes involved nucleophilic addition-electrophilic coupling cascade by iminium catalysis (* indicates stereogenic centers potentially produced in these processes).

The unique feature of the iminium catalysis is that the nucleophilic conjugate addition of the iminium species **9** leads to an electron-rich enamine **10**. The resulting enamine can be trapped by an electrophile to give iminium ion **11**. Hydrolysis releases catalyst **8** and accomplishes the nucleophilic addition-electrophilic coupling cascade sequence. Through rational design of substrates, a number of nucleophilic addition-electrophilic coupling cascades have been realized.[1,2]

4.02.2.1 Carbo-Nucleophiles with Carbo-Electrophiles

Nucleophilic addition-electrophilic coupling reactions using both carbo-based nucleophile and electrophile can generate at least two C–C bonds. Because the newly formed C–C bonds usually create contiguous stereogenic centers, they have afforded powerful tools for the assembly of useful chiral building blocks.

4.02.2.1.1 Discrete nucleophiles and electrophiles

Frechet and coworkers have demonstrated a one-pot multicomponent asymmetric cascade reactions catalyzed by soluble star polymers with highly branched noninterpenetrating catalytic cores (Scheme 3).[6] To overcome the incompatibility arising from acidic and basic catalysts, the soluble hyper-branched polymers are used to avoid undesired interactions. Catalysts **17** and **18** and catalyst **21** are encapsulated in noninterpenetrating star polymers to gain spatial compartmentalization and site isolation. As a result, the mixture of the individually imprisoned polymer organocatalysts can successfully catalyze the asymmetric cascade reactions without interference, which are not attainable by simple combination of otherwise incompatible catalysts. Moreover, because the strong acid **18** poisons the ability of enamine catalysis of **21**, the simple combination of the three small organic molecules in one pot cannot mediate the cascade reaction involving both nucleophilic addition and electronic coupling.

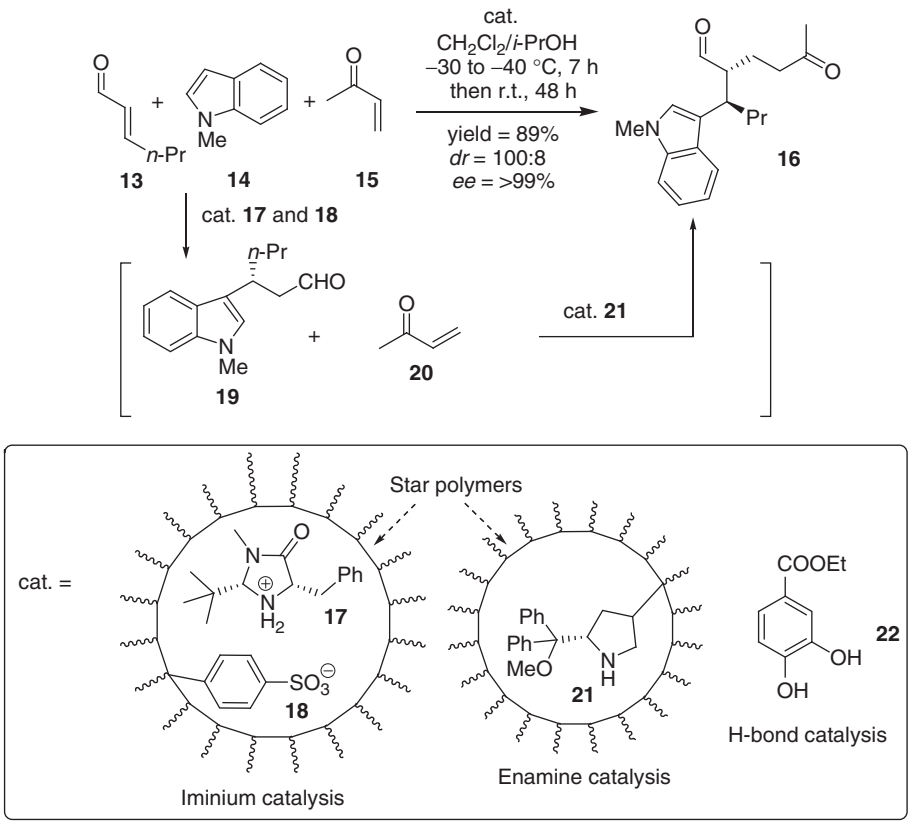
As demonstrated in this chapter, MacMillan's organocatalyst **17** and *para*-toluene sulfonic acid **18** as cocatalysts catalyze the Michael addition of indole **14** to enal **13** and catalyst **21** mediates the subsequent electrophilic coupling of the Michael adduct **19** with the electrophile enone **20**. It is noteworthy that although methyl vinyl ketone **20** is also a potential Michael acceptor, the aldehyde **13** is more reactive under the activation by **17**.

4.02.2.1.2 Integrated nucleophiles and electrophiles

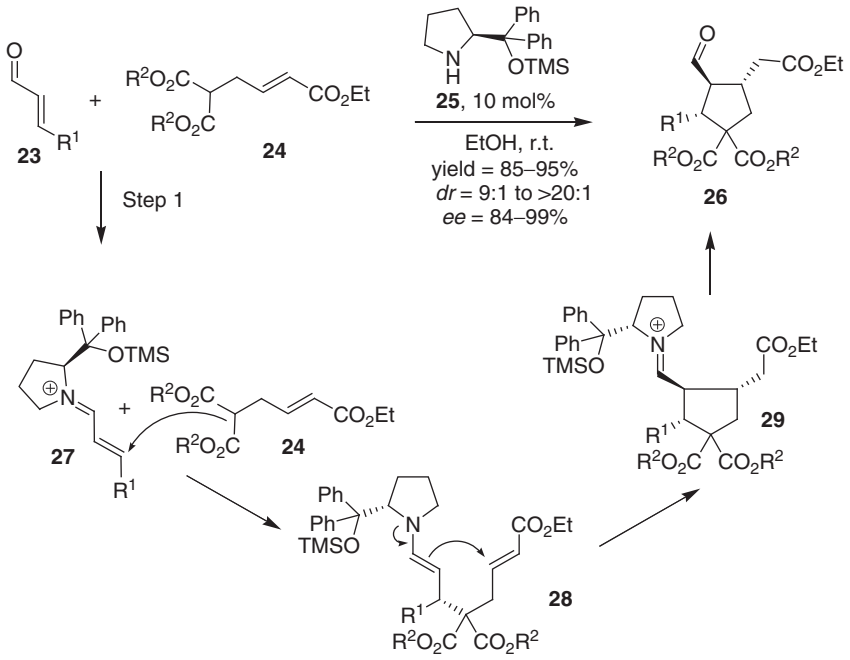
Wang and coworkers have schematized a double Michael addition cascade strategy by the incorporation of both carbon nucleophile and electrophile into one reactant (Scheme 4).[7] A malonate moiety serving a nucleophile is integrated with an electrophilic ethyl acrylate (**24**). In the cascade, the first Michael reaction takes place between the iminium species **27** derived from corresponding α,β-unsaturated aldehydes **23** and catalyst **25** and the malonate moiety in **24**. The resulting enamines **28** undergo the second Michael process with α,β-unsaturated ester intramolecularlly. The cascade process serves as a powerful approach to the multisubstituted functionalized chiral cyclopentane **26** in good yield as well as excellent diastereo- and enantio-selectivity. Notably, during the double Michael cycloaddition cascade, complex molecular architectures are rapidly constructed from simple starting materials, and two C–C bonds and three contiguous stereogenic centers are efficiently formed with fantabulous stereocontrols.

A similar approach was also demonstrated subsequently by Cordova and coworkers (Scheme 5).[8] A nitromlkane moiety is used instead of a malonate.

Moreover, using the similar strategy of integrating both carbo-based nucleophile and electrophile into 1,2-diones, Rueping and coworkers have formulated an asymmetric organocatalytic domino Michael-aldol reaction for the construction of

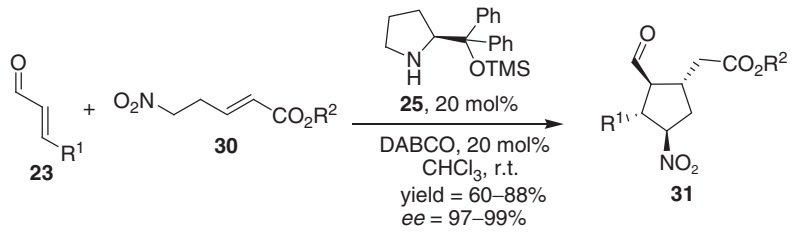


Scheme 3 Noninterpenetrating star polymers with incorporating chiral amine catalysts for one-pot cascade catalysis.

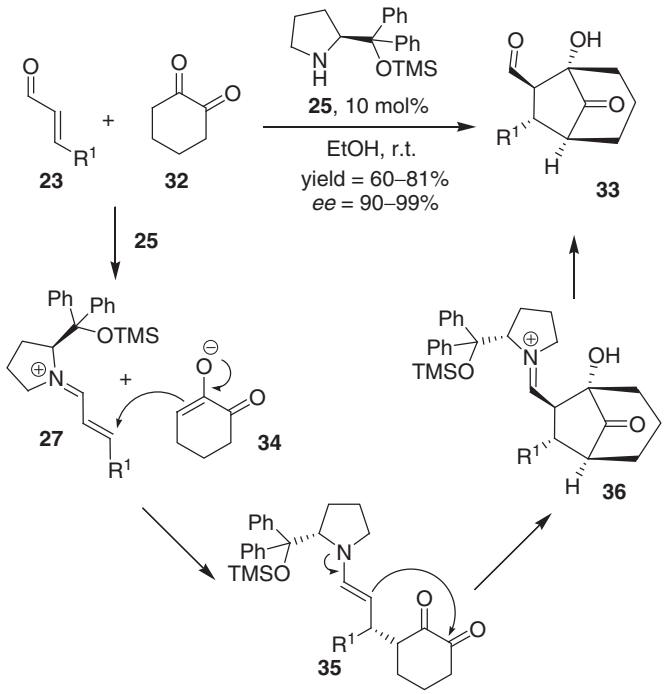


Scheme 4 Asymmetric organocatalytic double Michael cascade reactions.

polyfunctionalized chiral bicycle[3.2.1]octanes (Scheme 6).[9] 1,2-Cyclohexadione (**32**) serves as an electrophile thanks to the electronic withdrawing property of the diketone groups. In addition, the diketone renders the adjacent α-methene in **32** to be readily deprotonated as a nucleophile. Triggered by the initial Michael addition, the intramolecular aldol reaction that follows takes place to generate the bicyclic framework (**33**), which contains four stereogenic centers.



Scheme 5 Enantioselective organocatalytic nitro-Michael–Michael cascade reactions.

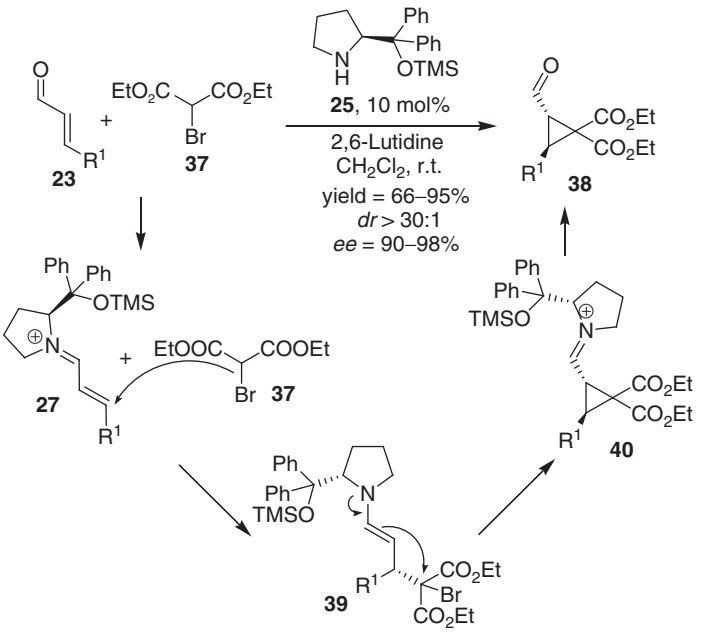


Scheme 6 Organocatalytic asymmetric Michael-aldol cascade reaction with 1,2-diketone.

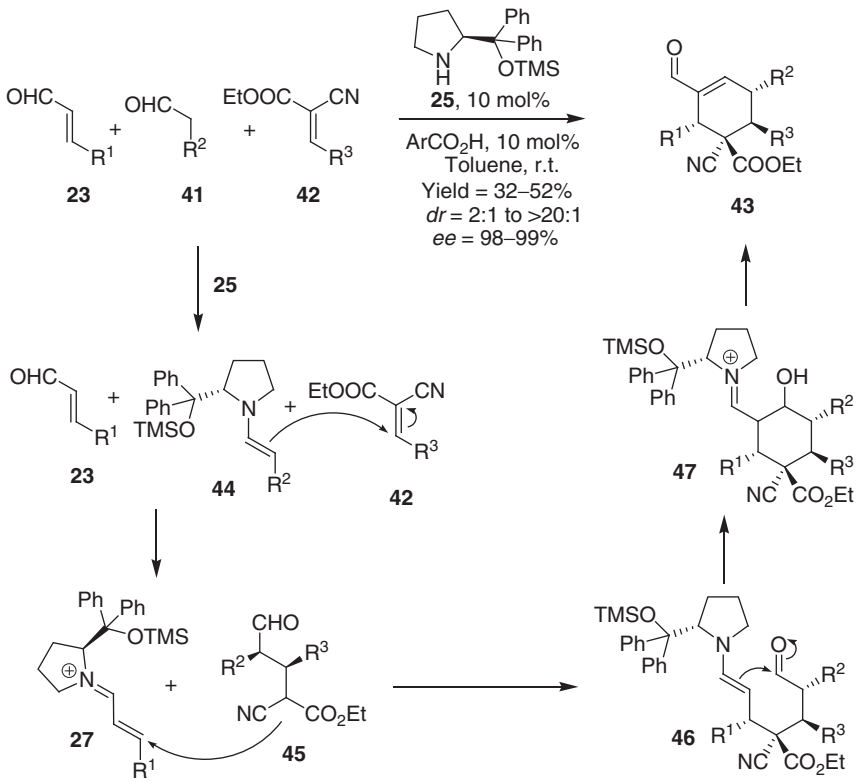
The same carbon can function as a nucleophile and as an electrophile. The implementation of the cascade produces a three-membered ring. Wang and coworkers have discovered an organocatalytic enantioselective cascade Michael-alkylation reaction for cyclopropanation (Scheme 7).[10] The bromo-malonate **37** is designed as the integrated nucleophile and electrophile. The nucleophilic malonate moiety serves as the Michael donor, whereas the bromine serves as a leaving group under the intramolecular nucleophilic attack. The initial Michael addition induces intramolecular alkylation to generate the chiral tetra-substituted cyclopropanes **38**. The merit of the cascade process is highlighted by its high efficiency in the production of two C–C bonds, two contiguous stereogenic centers, and one quaternary carbon center from simple starting materials.

4.02.2.1.3 In situ *generated bifunctional intermediates*

In some cases, the requisite nucleophile and electrophile attacking or being attacked by α,β-unsaturated aldehyde substrates are not preexisted in reactants. In such a circumstance, a bifunctional intermediate, which integrates both nucleophilic moiety as well as electrophilic moiety, can be *in situ* generated. The strategy is vividly embodied by the asymmetric organocatalytic triple-cascade reaction discovered by Melchiorre and coworkers (Scheme 8).[11] The bifunctional intermediate **45** is *in situ* generated by the Michael addition reaction between the enamine **44** derived from aldehyde **23** and the Michael acceptor **42**. In the intermediate **45**, the enolizable nitrile eater serves as the nucleophile for the conjugate addition that follows, whereas the aldehyde moiety serves as the electrophile. The intermediate **46** is yielded from a Michael reaction of **45** and iminium species **27**. A subsequent intramolecular aldol reaction through electrophilic coupling transforms into cyclohexene carbaldehydes **43**. The organocatalytic enamine-iminium-enamine cascade sequence provides a flexible and direct access to enantiopure cyclohexanes bearing four contiguous chiral centers including one all-carbon quanternary stereogenic center.

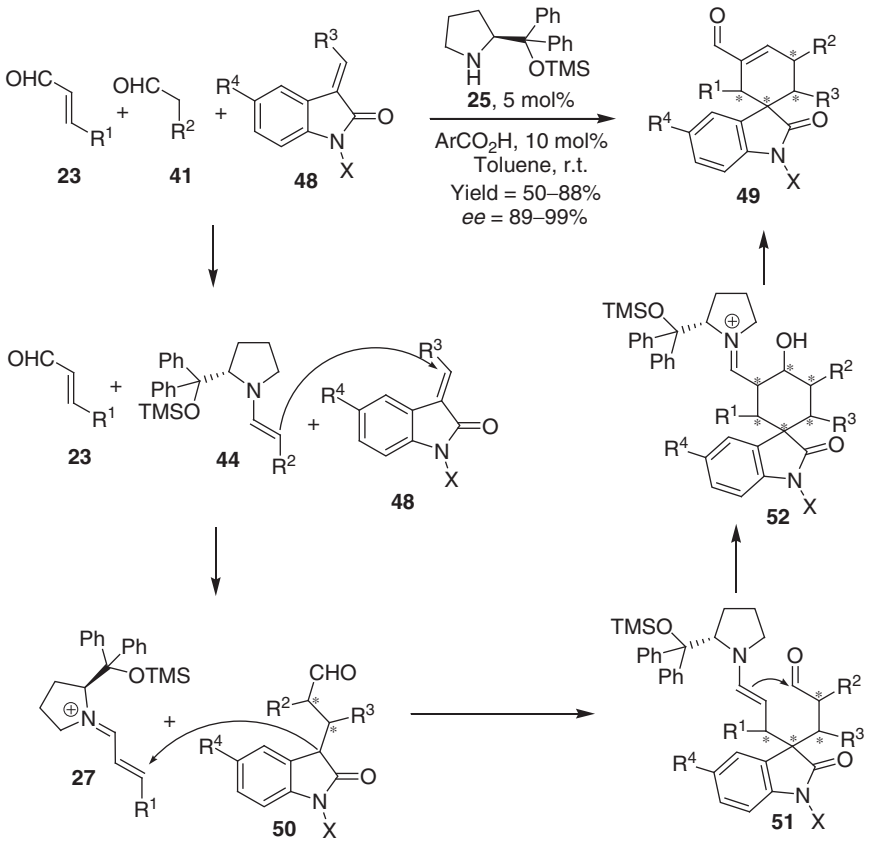


Scheme 7 Organocatalytic enantioselective cyclopropanation by a domino Michael-alkylation.



Scheme 8 Enantioselective organocatalytic enamine–iminium–enamine cascade reaction.

Chen and coworkers have developed an organocatalytic tandem reaction to construct six-membered spirocyclic oxindoles **49** using a similar strategy (Scheme 9).[12] Due to the electronic withdrawing property of the cyclic amide, oxindoles **48** serve as Michael acceptor. The *in situ* generated bifunctional intermediate **50** consists of the oxindole nucleophilic moiety and the aldehyde electrophilic moiety.



Scheme 9 Organocatalytic enantioselective cascade approach to spirocyclic oxindoles.

4.02.2.1.4 Integrated substrates and electrophiles

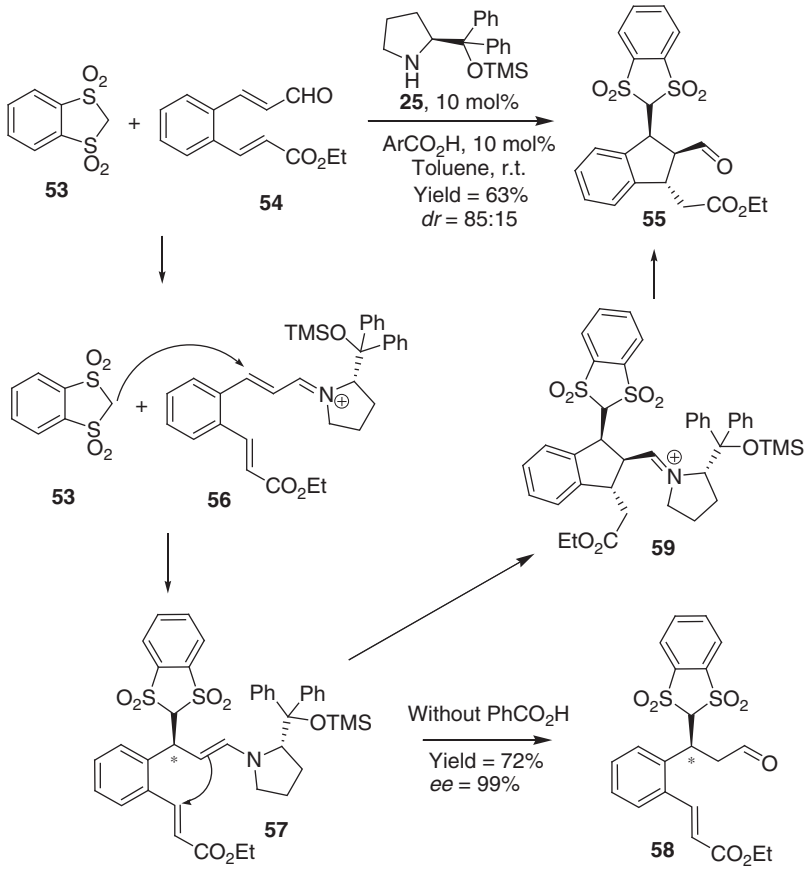
When the electrophile is integrated into an α,β-unsaturated aldehyde framework, intramolecular cyclization-electrophilic coupling can occur after the enal is attacked by foreign nucleophile. Palomo and coworkers successfully expand the chemistry of germinal bis(sulfone)s by utilizing such a strategy (Scheme 10).[13] Compound **54** is designed to bear both α,β-unsaturated aldehyde and ester moieties. The cyclic germinal bis(sulfone) **53** serves as foreign nucleophile. It is noted that without benzoic acid, the reaction stops after the initial Michael addition, and product **58** is identified with 99% *ee*. With benzoic acid, the tandem intramolecular electrophilic coupling proceeds after the nucleophilic addition, and the chiral trisubstituted indane **55** is obtained.

4.02.2.1.5 Integrated substrates, nucleophiles, and electrophiles

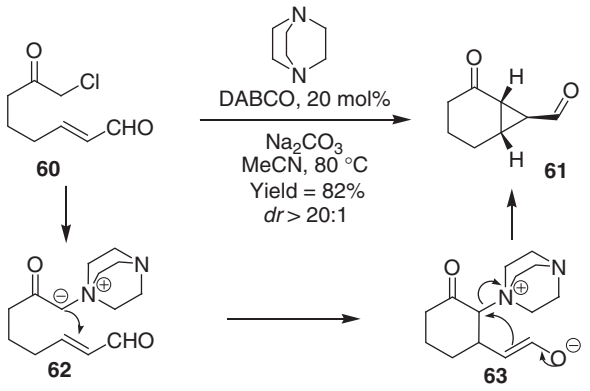
Gaunt and coworkers have disclosed an intramolecular organocatalytic cyclopropanation methodology with three reactive sites α,β-unsaturated aldehyde, nucelophile, and electrophile in one compound **60** (Scheme 11).[14] Different from previously discussed activation mode, the cascade process is catalyzed by tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO). Initially, the amine DABCO displaces the chloride in **60** to give the ammonium ylide **62**. The intramolecular conjugate addition that follows produces the enolate intermediate **63**, which is readily available for the tandem electrophilic alkylation by displacement of the ammonium group. The [6.1.0]bicycloalkane **61** is produced as the single diastereoisomer in good yield. By altering the linker length, versatile [*n*.1.0]bicycloalkanes, which possess three stereocenters, two new C–C bonds and two rings can be stereoselectively synthesized in a single transformation.

4.02.2.2 Carbo-Nucleophiles with Heteroatom-Electrophiles

Besides C–C bonds, the formation of C-heteroatom bonds is also an important aspect in organic synthesis. The strategy of nucleophilic addition-electrophilic couplings provides an effective solution to construct multiple C-heteroatom bonds in one pot.



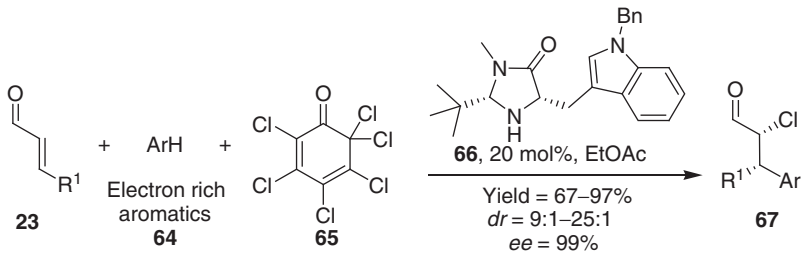
Scheme 10 Michael–Michael approach to trisubstituted indanes initiated by conjugate addition of bis(sulfone).



Scheme 11 An intramolecular organocatalytic cyclopropanation.

4.02.2.2.1 Carbo-nucleophiles with halogenated electrophiles

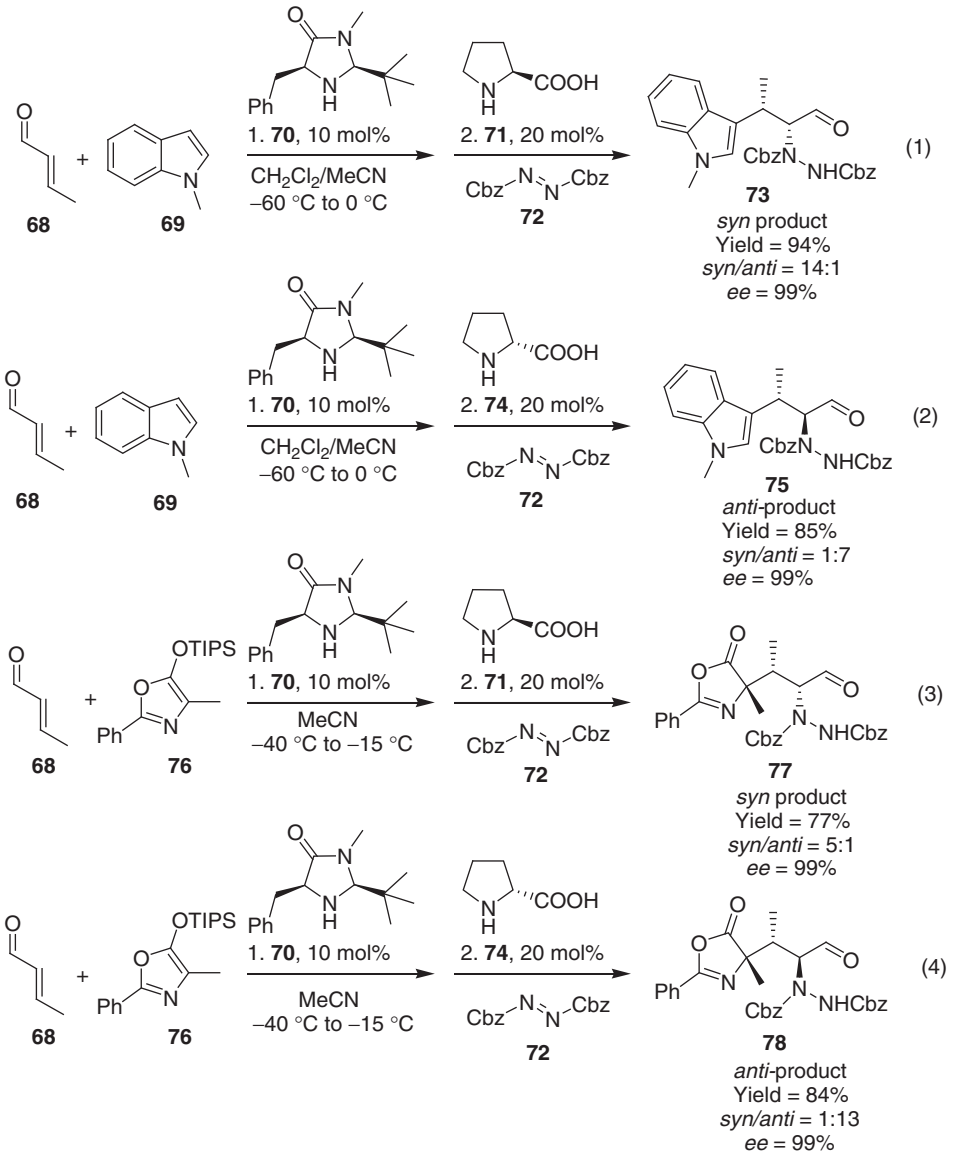
MacMillan and coworkers have developed an enantioselective organo-cascade catalysis that enables the construction of carbo-halogen bond and carbo-carbon bond based on a strategy described in Scheme 12.[15] The cascade process is triggered by the iminium activated Michael addition reaction by organocatalyst **66**, in which electron-rich aromatics **64** serve as Michael donor. Following the similar mechanism described previously, the Michael adduct intermediate enamines are trapped by an electrophile. In this case, chlorinated quinine **65** provides electrophilic chlorine. α,β-Bifunctionalized aldehydes **67** are received in excellent enantio-purity. The strategy has also been extended to other types of carbo-heteroatom bond formation in their studies.



Scheme 12 Enantioselective organo-cascade catalysis with halogen-based electrophile.

4.02.2.2.2 Carbo-nucleophiles with aza-electrophiles

MacMillan and coworkers have also discovered a cycle-specific organo-cascade catalysis protocol to carry out asymmetric olefin arylamination/alkyamination (Scheme 13).[16] Carbon-based nucleophiles **68** and **76** are used to trigger the initial Michael addition by MacMillan catalyst **70**. The aza-electrophile dibenzylazodicarboxylate **72** together with enamine catalyst proline L-**71** and D-**74** are submitted to reaction mixture to extend the tandem process to the degree of electrophilic coupling. A good feature of the process is that absolute stereo-configuration of stereogenic centers of products can be deliberately controlled by using different



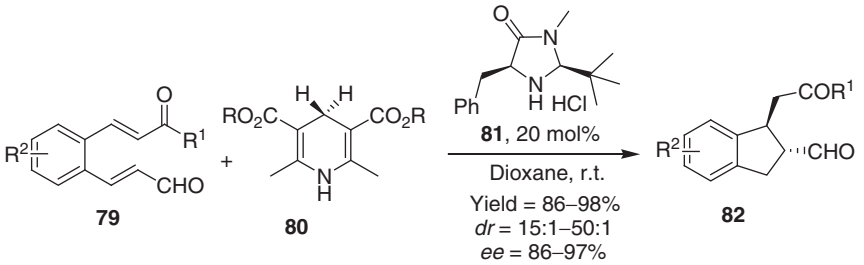
Scheme 13 Enantioselective cycle-specific cascade catalysis with nitrogen-based electrophiles.

catalysis combinations. As demonstrated, when L-proline **71** is used during the enamine catalysis, the *syn* product is isolated in preference with 99% *ee* (equations 1 and 3). If D-proline **74** is applied, the *anti*-product is identified as the single enantio-isomer (equations 2 and 4).

4.02.2.3 Hydride-Nucleophiles with Various Electrophiles

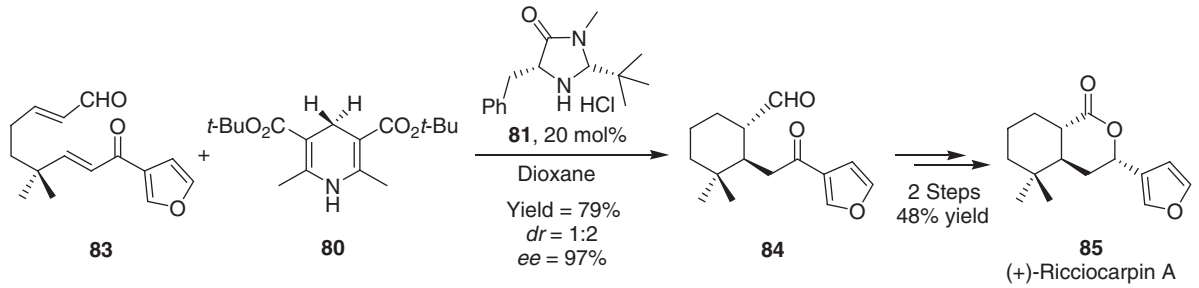
4.02.2.3.1 Hydride-nucleophiles with carbo-electrophiles

Hydride is the smallest nucleophile in organic synthesis, and Hantzsch ester is often used as a typical hydride donor in organo-catalysis. List and coworkers have developed a highly enansioselective organocatalytic reductive cyclization of enal enones (Scheme 14).[17a] The reaction proceeds via an iminium conjugated reduction followed by an enamine Michael cyclization. The Hantzsch ester **80** functions as the hydride Michael donor, which triggers the cascade process. Intramolecular electrophilic Michael addition happens spontaneously with the help of the integrated structural design of α,β-unsaturated aldehyde and enone moieties in one compound **79**.



Scheme 14 Enantioselective organocatalytic reductive Michael cyclization of enal enones.

List and Michrowska have employed the same reductive Michael-cyclization strategy in the total synthesis of (+)-ricciocarpin A **85**, which is a furanosesquiterpene lactone (Scheme 15).[17a] The α,β-unsaturated aldehyde is tethered with the enone moiety, which function as electrophilic Michael acceptor. Mediating by MacMillan imidazolidinone catalyst **81**, six-membered cyclization product **84** is assembled. The compound **84** can be directly transferred to the natural product **85** in two steps with 48% overall yield.



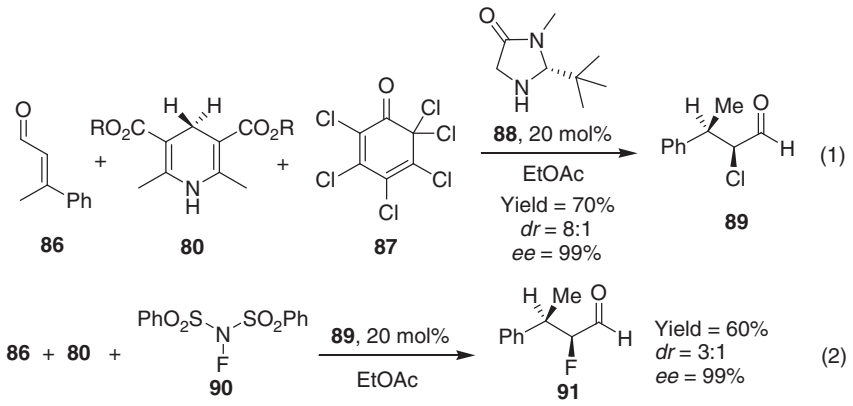
Scheme 15 Synthesis of (+)-ricciocarpin A via a reductive Michael cyclization cascade.

4.02.2.3.2 Hydride-nucleophiles with halogen-electrophiles

MacMillan and coworkers have revealed an enantioselective organo-cascade catalysis to functionalize β,β-disubstituted enals **86** (Scheme 16).[15] In the asymmetric hydro-halogenation cascade, the Hantzsch ester **80** serves as hydride donor in the initial nucleophilic Michael addition step, and chlorinated quinine **87** or fluorinated reagent **90** is used as acceptor in the tandem electrophilic coupling step. Catalyst **88** shows superior catalytic ability that fosters the fast consumption of nucleophile before the electrophilic addition that follows, and also prevents the neutralization process involving the reaction of nucleophile and electrophile to form hydro-halogen, such as HCl or HF.

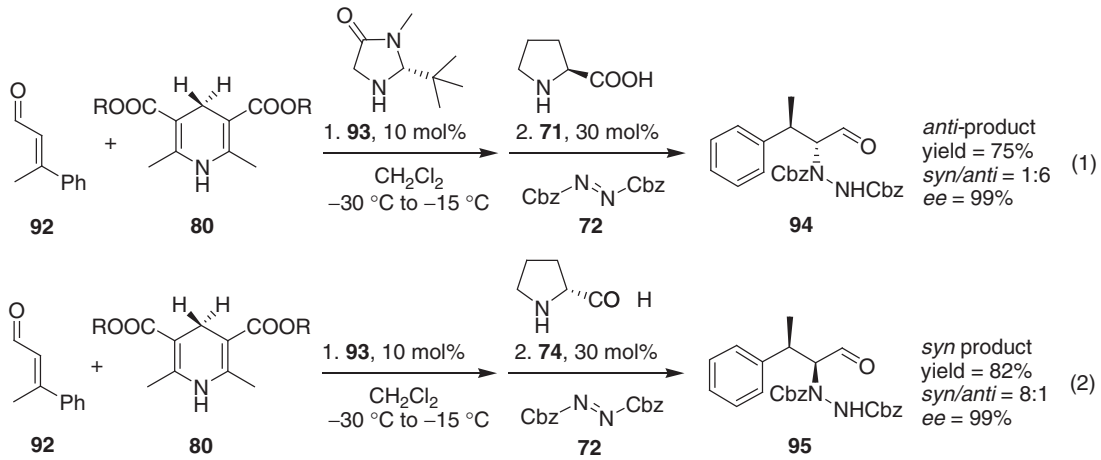
4.02.2.3.3 Hydride-nucleophiles with aza-electrophiles

MacMillan and coworkers have also successfully extended the cycle-specific enantioselective organo-cascade protocol from olefin aryl-/alkyl-amination (Scheme 14) to hydro-amination using hydride nucleophile (Scheme 17).[16] The hydrogenation–amination



Scheme 16 Enantioselective organocatalytic hydro-halogenation of β,β-disubstituted enals.

sequence using the combination of catalysts **85** and **71** or **74** provides the α,β-bifunctionalized aldehyde products with nearly perfect enantiocontrol and excellent diastereoselectivity. By using the different enantiomers of the proline catalyst L-**71** or D-**74** while retaining the imidazolidinone catalyst **85**, both *anti*- and *syn*-diastereoisomers **94** and **95** can be obtained in complete reversal of diastereocontrol without loss in reaction efficiency or enantioselectivity.



Scheme 17 Enantioselective organocatalytic hydro-amination of β,β-disubstituted enals.

4.02.2.4 Aza-Nucleophiles with Various Electrophiles

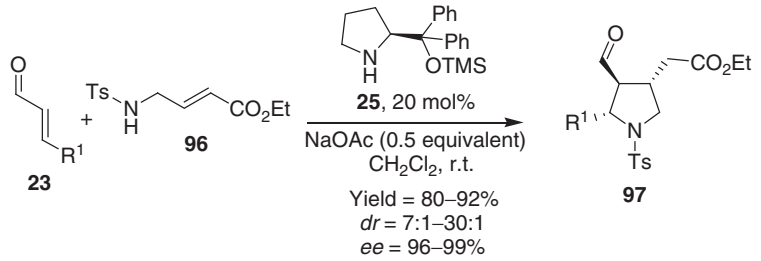
Generally speaking, nitrogen centered nucleophiles are not as widely employed as carbo-nucleophiles for conjugate additions as well as various other transformations. One of the major reasons is their weaker nucleophilicity. Another drawback arises from its interference with catalysts. In metal-based catalyst systems, the nucleophilicity and basicity of nitrogen usually renders it as a decent binding site for metal ion, and hence decreases the reactivity of the nucleophile and the Lewis acidity of the metal catalyst. In a system involving amine-base organocatalyst, if the reactivities of the aza-containing reactant and the catalyst are not properly tuned and balanced, the stoichiometric amount of aza-nucleophiles has a potential to poison catalytic cycle by competitively binding with carbonyl substrates.

The strategy of nucleophilic addition tandem with electrophilic coupling can be employed as a solution to overcome these shortcomings. Since the intermediate resulting from a nucleophilic addition is swiftly consumed by the electrophilic coupling that follows, the tandem process potentially increases the reactivity of substrate by dragging the reaction to completion.

4.02.2.4.1 Aza-nucleophiles with carbo-electrophiles

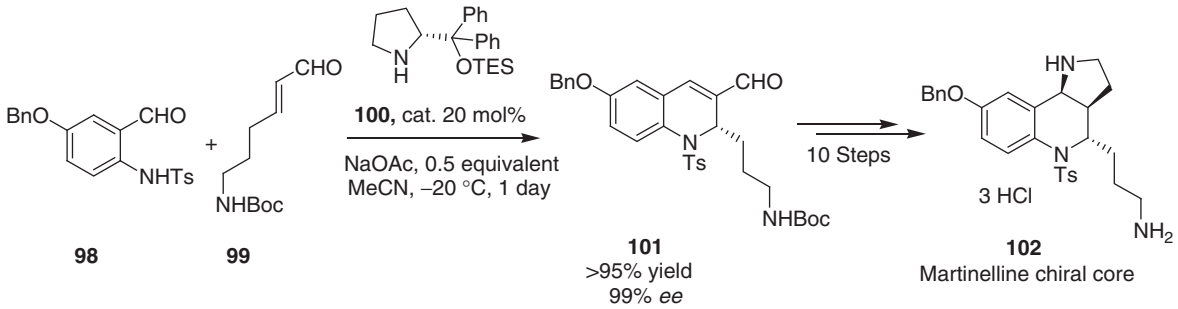
Wang and coworkers have documented a highly enantio- and diastereo-selective organocatalytic aza-Michael–Michael cascade reaction for the one-pot synthesis of chiral trisubstituted pyrrolidines (Scheme 18).[18] The aza-nucleophile is intentionally integrated with electrophilic α,β-unsaturated ester moiety in **96** to foster the fast intermediate trapping cyclization cascade. The structural

mapping of the bifunctional reactant **96** is following the same designed strategy developed by the same group (see Scheme 4). The *N*-protecting group has been carefully scrutinized to fit the desired cascade process, and the tosyl (Ts) group is selected as an effective one. The electronic withdrawing property of the protecting group diminishes the nucleophilicity as well as basicity of the nitrogen atom without compromising its ability to trigger the initial aza-Michael addition. The functionalized multisubstituted chiral pyrrolidine that contains three contiguous stereogenic centers serves as an important synthetic scaffold for further elaboration.



Scheme 18 Organocatalytic aza-Michael–Michael cascade reaction.

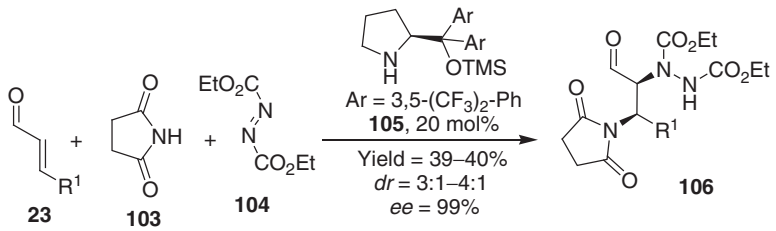
Hamada and coworkers have achieved the asymmetric synthesis of the dihydroquinoline **101**, which leads to the martinelline chiral core **102** in 10 steps (Scheme 19).[19] The aza-Michael tandem aldol condensation cascade uses 4-methoxycarbonylanthranilaldehyde **98** and the aza-containing α,β-unsaturated aldehyde **99** as substrates. After screening of various aminocatalysts as well as solvents, reaction conditions are optimized, and the dihydroquinoline **101** is received in almost quantitative yield and 99% *ee*. Based on the cascade strategy, the first enantioselective synthesis of the martinelline chiral core **102** and the formal total syntheses of martinellic acid and martinelline are developed.



Scheme 19 The formal synthesis of martinelline using aza-Michael tandem aldol condensation cascade.

4.02.2.4.2 Aza-nucleophiles with discrete aza-electrophiles (diamination)

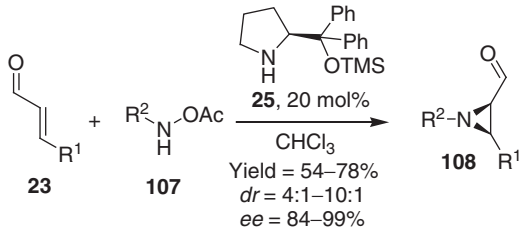
Both nucleophile and electrophile can be nitrogen based. If the two aza-moieties are not integrated in one reactant, a synthetically useful α,β-diaminated product is delivered. Jorgensen and coworkers have presented an organocatalytic one-pot *syn* diamination of α,β-unsaturated aldehydes **23** by using succinimide **103** as the nucleophile and diethyl azodicarboxylate **104** as the electrophile (Scheme 20).[20] The α,β-*syn*-diaminated aldehydes **106** are obtained in good yields and with high diastereo- and enantioselectivities. Cleavage of the azodiacarboxylate moiety leads to synthetically important chiral diamines.



Scheme 20 Organocatalytic asymmetric *syn* diamination reaction.

4.02.2.4.3 Aza-nucleophiles with integrated aza-electrophiles (aziridination)

Similarly, if both the aza-nucleophile and aza-electrophile are integrated into one reactant, the aziridination proceeds. Cordova and coworkers have reported a highly chemo- and enantio-selective organocatalytic aziridination of α,β-unsaturated aldehydes (Scheme 21).[21] The electrophilicity of the aza-electrophile moiety in **107** is modulated by the acetate substituent, which also serves as a good leaving group in the subsequent intramolecular enamine alkylation step. The aziridination follows similar strategy as the carbon-based cyclopropanation (see Scheme 7). The cascade process is catalyzed efficiently by simple chiral pyrrolidine derivative **25** and gives the corresponding 2-formylaziridines **108** in good-to-high yields and with decent diastereo- and enantio-selectivities. The synthetic utility of the aziridination protocol is demonstrated in an asymmetric synthesis of β-amino acid esters after ring-opening of the chiral aziridines **108**.[21] Additionally, synthetically useful asymmetric *trans*-aminohydroxylation products can also be obtained after reduction of chiral aziridines.[22]



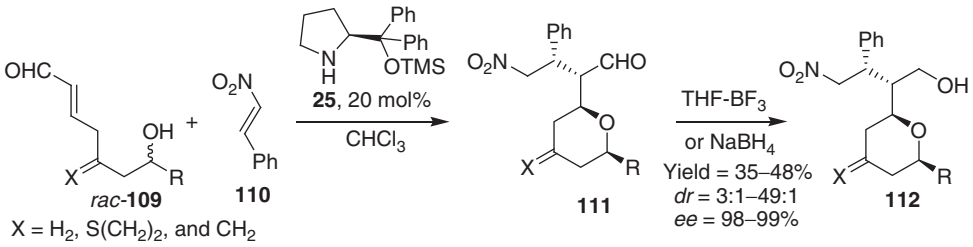
Scheme 21 Organocatalytic enantioselective aziridination of α,β-unsaturated aldehydes.

4.02.2.5 Oxa-Nucleophiles with Various Electrophiles

Due to its much weaker nucleophilicity, oxygen-based nucleophile is less widely employed in the cascade strategy comparing with carbon- and nitrogen-based ones. Generally, enantioselective oxa-Michael additions of alcohols to α,β-unsaturated aldehydes are complicated by their reversibility, which can lead to low yields and selectivities. By incorporating oxa-Michael addition step to subsequent electrophilic coupling step, the intermediate of Michael adduct is trapped and consumed, and the equilibrium lies largely toward the product. As a result, the issue should be overcome. Because of its synthetic importance, epoxidation using integrated oxa-nucleophile and oxa-electrophile is broadly studied, a process similar to aziridination.

4.02.2.5.1 Oxa-nucleophiles with carbo-electrophiles

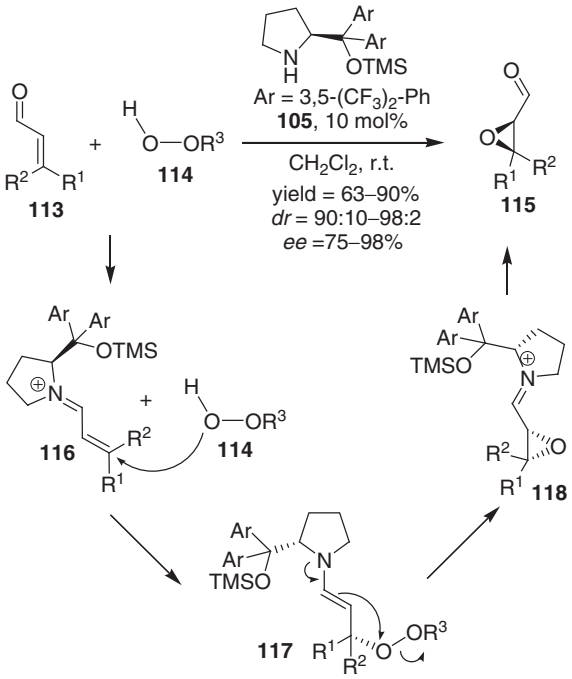
Brenner-Moyer and coworkers have reported an organo-cascade kinetic resolution of racemic alcohols **109**, which provides access to enantioenriched functionalized tetrahydropyrans **112** (Scheme 22).[23] The organo-cascade is initiated by intramolecular oxa-Michael addition that is highly selective but rapidly reversible. The product of the iminium-catalyzed conjugate addition undergoes a kinetic resolution, followed by a subsequent enamine-catalyzed intermolecular reaction with *trans*-β-nitrostyrene **110**, which is used as an electrophile to trap and resolve racemic oxa-Michael adducts from **109**.



Scheme 22 Organo-cascade kinetic resolution.

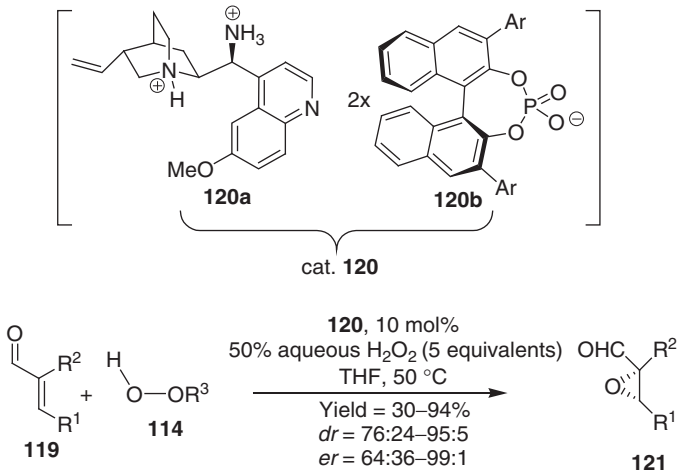
4.02.2.5.2 Oxa-nucleophiles with oxa-electrophiles (epoxidation)

Because of the high value of epoxides in organic synthesis, asymmetric epoxidation occupies a prominent position in catalysis. Jorgensen and coworkers have developed the first organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes using catalyst **115** and peroxide **114** as the oxidant (Scheme 23).[24] The iminium ions **116** by association of enals **113** with the chiral amine **105** trigger a Michael addition of peroxide **114** to lead to an enamine intermediate **117**. The formation of the epoxides **118** takes place by attack of the enamine species to the electrophilic peroxygen atom. Chiral α,β-epoxy aldehydes **115** are obtained with good yield and high diastereo- and enantio-selectivity.



Scheme 23 Organocatalyzed epoxidation of enals with peroxides.

List and coworkers have also presented an asymmetric catalytic epoxidation of α-branched α,β-unsaturated aldehydes (Scheme 24).[25] Although it is more challenging for the direct epoxidation of α-branched enals than linear ones, a highly synergistic combination of a primary cinchona-based amine **120a** and a chiral phosphoric acid **120b** was found to promote the reaction with decent efficiency as well as excellent stereocontrol. The catalysis pathway mediated by the synergic chiral salt **120** follows the same catalytic pattern as that of secondary amine catalyst **105**. In the proposed transition state of the initial Michael addition, a contact ion pair that consists of chiral primary amine-derived iminium cation and chiral phosphate anion fosters escalated reactivity and synergic delivery of peroxide nucleophile through hydrogen bonding. Synthetically useful asymmetric *trans*-dihydroxylation products can be directly obtained after reduction of chiral epoxides.[22]

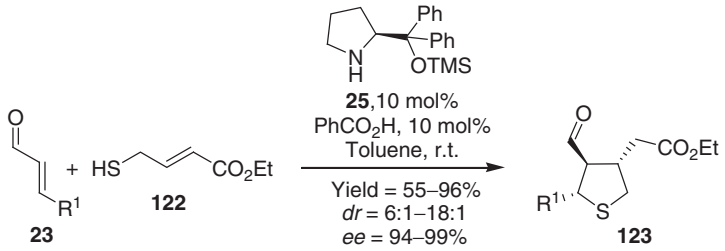


Scheme 24 Catalytic asymmetric epoxidation of α-branched enals.

4.02.2.6 Sulfur-Nucleophiles with Carbo-Electrophiles

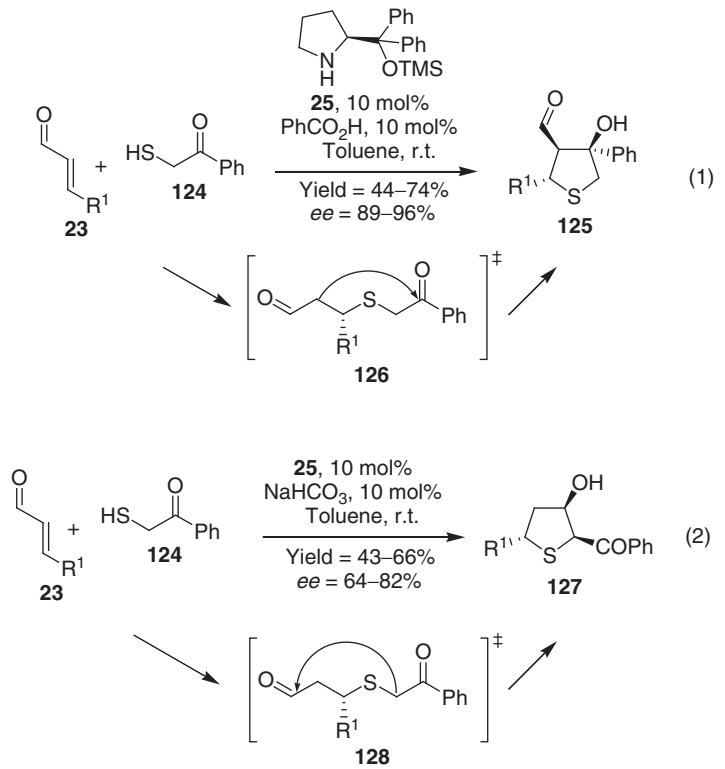
Thiols are more nucleophilic than alcohols. Moreover, the soft Lewis basicity of sulfur-nucleophile usually renders it more compatible with soft electrophilic β-carbon of Michael donor in conjugate additions. Wang and coworkers have developed an

organocatalytic enantioselective domino thio-Michael–Michael reaction of α,β-unsaturated aldehydes **23** with ethyl 4-mercapto-2-butenoate **122** (Scheme 25).[26] The electrophilic α,β-unsaturated ester is used to trap the enamine from the first thio-Michael addition. The cascade process promoted by chiral diphenylprolinol TMS ether **25** furnishes highly functionalized chiral tetrahydrothiophenes **123** with three stereogenic centers in high enantio- and diastereo-selectivities.



Scheme 25 Organocatalytic asymmetric domino thio-Michael–Michael reaction.

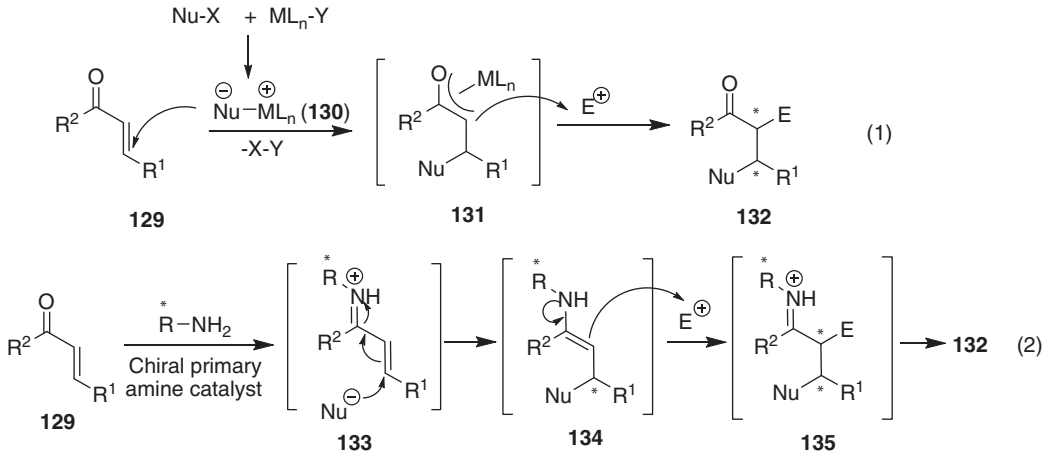
Using a similar strategy, Jorgensen and coworkers have developed an asymmetric organocatalytic domino reaction for synthesis of highly functionalized optically active tetrahydrothiophenes (Scheme 26).[27] The catalytic domino reaction can be chemoselectively controlled by selection of acidic or basic additive. If acidic additive, such as benzoic acid, is added in the reaction, tetrahydrothiophene carbaldehydes **125** are obtained in good yields and with excellent enantio- and diastereoselectivity (equation 1). The reaction proceeds via the sequence of iminium activated thio-Michael addition tandem enamine-catalyzed aldol addition toward electrophilic ketone moiety in **124**. When basic additive, such as sodium bicarbonate, is used in the same system, (tetrahydrothiophenes-2-yl)phenyl methanones **127** are identified in moderate yields and with very good selectivities (equation 2). The asymmetric domino process also runs via a similar thio-Michael-aldol cascade. However, in this circumstance, the aldol reaction does not flow from the enamine-activated α-carbon of aldehydes **23** to electrophilic ketone moiety **124**, as shown in intermediate **126**, instead the reaction is from the base-activated α-carbon of phenylketo **128** to aldehyde moiety **23**.



Scheme 26 Asymmetric synthesis of functionalized tetrahydrothiophenes by organocatalytic domino reactions.

4.02.3 The α,β-Unsaturated Ketones

When α,β-unsaturated ketones are used as substrates for nucleophilic addition-electrophilic couplings, Lewis acids as catalysts are much more widely employed than organocatalysts (Scheme 27). The majority of methods for Lewis acid-catalyzed conjugate addition carbonmetallative enolate **130** trapping require an external electrophile to complete the cycle.[28] A true carbonmetallative cascade process in one-pot fashion is uncommon, and is in need of extensive development.[28,29] In Lewis acid-catalyzed cascade reactions, before nucleophilic addition, the transmetallation step usually happens first, in which nucleophilic moiety originally from organometallic reagent transfers to and coordinates with the metal center M. The nucleophile is activated by the metal complex and delivered to Michael acceptor **129**. The resulting enolate **131** is then trapped by an electrophile, and results in α,β-bifunctionalized ketone **132**. Various chiral ligands are usually used in the appropriate catalytic systems to achieve asymmetric catalysis.



Scheme 27 Lewis acid and chiral primary amine-catalyzed conjugate addition-electrophilic coupling of enone substrates (* indicates stereogenic centers potentially produced in these processes).

In organocatalysis, although chiral secondary amines are generally used to catalyze cascade reactions of α,β-unsaturated aldehydes, primary amines are more efficiently paired with α,β-unsaturated ketones to realize activation and stereocontrol (Scheme 27, equation 2).[30] Hydrogen bonding catalysts, such as chiral thioureas or alkaloids, are also employed in the activation of enones.[31] Due to steric hindrance as well as decreased electrophilicity of ketone carbonyl carbon, chiral secondary amine cannot effectively associate with ketone to generate iminium species **133**. The chiral primary amine-catalyzed cascade reaction also follows the sequence of iminium activated nucleophilic addition tandem enamine-catalyzed electrophilic trapping.

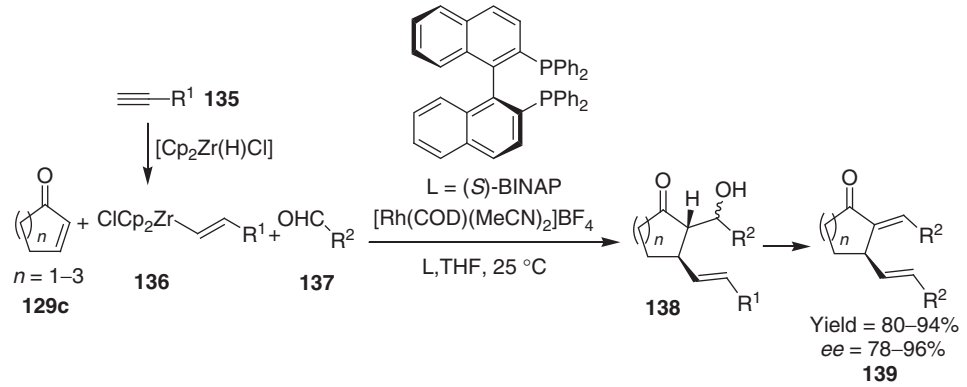
4.02.3.1 Carbo-Nucleophiles with Carbo-Electrophiles

4.02.3.1.1 Discrete nucleophiles and electrophiles

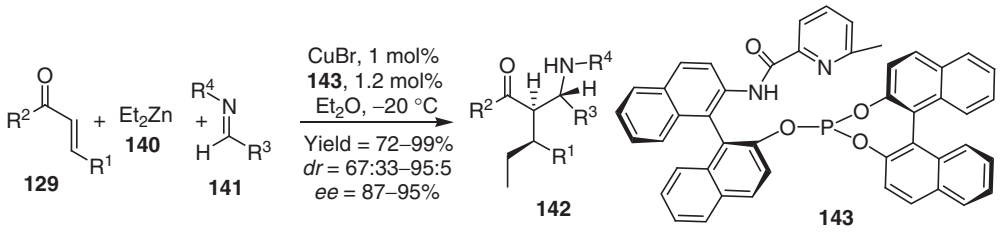
Nicolaou and coworkers have discovered a catalytic asymmetric three-component Michael-aldol cascade reaction of cyclic enones **129c**, and have applied the methodology in enantioselective synthesis of the spirocyclic system of marine natural product vannusal A (Scheme 28).[32] Different from above-mentioned Krische's approach, cyclic enones **129c**, nucleophilic alkynes **135**, and electrophilic aldehydes **137** are used in the cascade strategy without interference with each other. Nucleophilic vinyl zirconium organometallic species **136** is *in situ* generated from **135** with zirconium complex. In the presence of chiral rhodium complex, cyclic enones **129c** are transferred into α,β-bifunctionalized ketones **138**, which can be conveniently converted to products **139**, useful building blocks for further manipulation in natural product synthesis.

Huang and coworkers have developed an efficient asymmetric tandem conjugate addition-Mannich cascade process for the construction of multiple contiguous acyclic stereogenic centers with high diastereo- and enantio-selectivity (Scheme 29).[33] As complementary to Nicolaou's work, acyclic α,β-unsaturated ketones **119** are used as substrate. Stereo-selectively controlled by chiral ligand **143**, the cascade reaction is triggered by copper-catalyzed conjugate addition of diethyl zinc reagent **140** to acyclic unsaturated carbonyl compound. The *in situ* generated chiral zinc-enolate is trapped by electrophilic *N*-protecting aldimine **141** to yield final products **142**.

Although the hard nucleophile, such as organolithium reagent, is ready for 1,2-addition to carbonyl groups, it can still be used in conjugate addition under specifically tuned conditions. Yamamoto and coworkers have demonstrated that strong

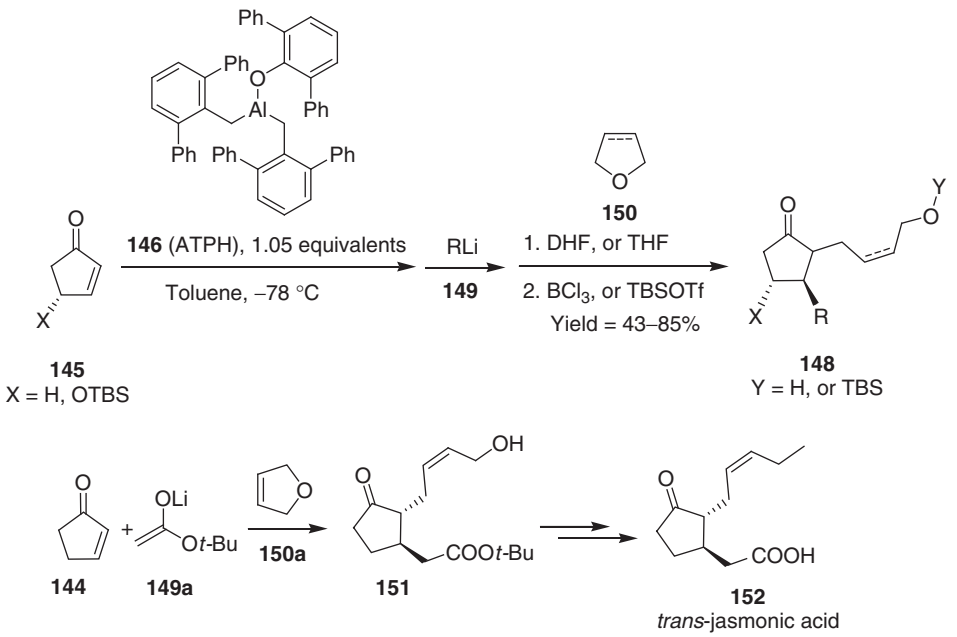


Scheme 28 Catalytic asymmetric three-component Michael-aldol reaction of cyclic enones.



Scheme 29 Copper-catalyzed tandem Michael–Mannich cascade reaction of acyclic enones.

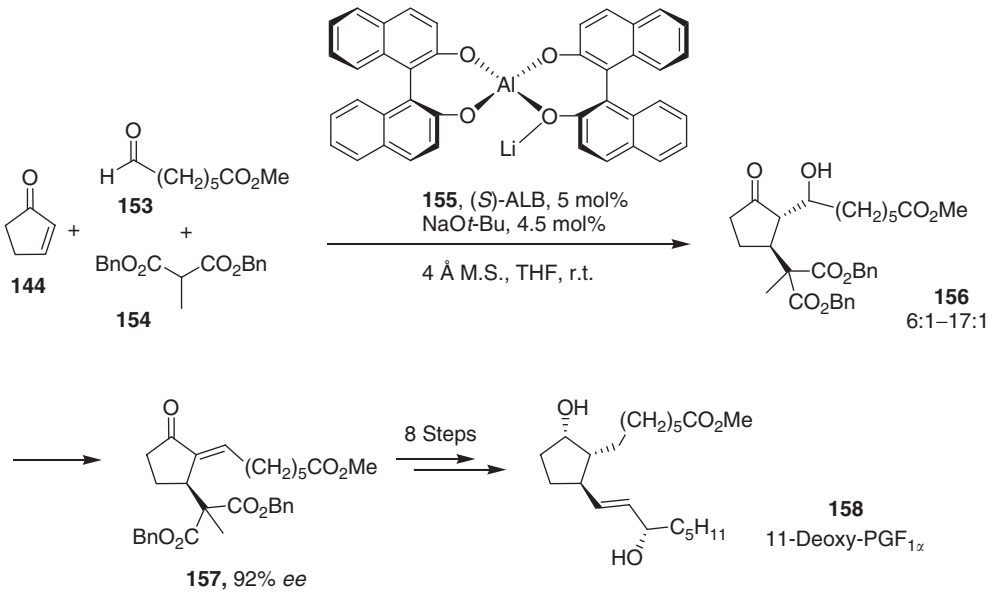
organolithium reagents **149** can be used as soft nucleophile in conjugate addition by using stoichiometric amount of sterically hindering ATPH (**146**) to precomplex the carbonyl of enones **145** (Scheme 30).[34] The resulting metal enolate can be trapped *in situ* with BCl_3 activated electrophile, such as THF and DHF. This three-component methodology can provide the *trans*-disubstituted cyclopentanone product **148a**, which is ready for the synthesis of *trans*-jasmonic acid **152** in just a few steps.



Scheme 30 Three-component cascade process using organolithium reagent in conjugate addition.

Shibasaki and coworkers have reported an elegant asymmetric total synthesis of 11-deoxy-$PGF_{1\alpha}$ **158** using the three-component Michael-aldol cascade as a key strategy (Scheme 31).[35] The cascade reaction is efficiently promoted by a

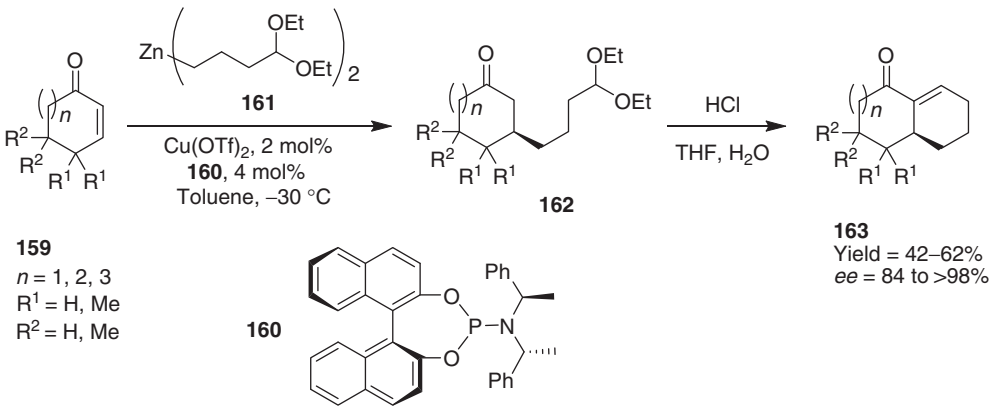
heterobimetallic asymmetric complex (ALB) **155** to give the condensation product **157** at room temperature in 92% *ee* and 84% yield, which is converted to 11-deoxy-$PGF_{1\alpha}$ **158** after several steps. The unique heterobimetallic complex **155** is a multifunctional asymmetric catalyst, showing both Brønsted basicity and Lewis acidity to deliver synergic activations of multiple substrates.



Scheme 31 Catalytic asymmetric synthesis of 11-deoxy-$PGF_{1\alpha}$ using the three-component Michael-aldol condensation sequence.

4.02.3.1.2 Integrated nucleophiles and electrophiles

Electrophile can be introduced by using functionalized dialkylzinc reagent, such as an acetal moiety, which serves as a protected aldehyde. By using functionalized organozinc reagent **161**, Feringa and cowrkers have demonstrated the catalytic enantioselective annulations via conjugate addition tandem aldol cyclization (Scheme 32).[36] The aldehyde functionality is protected as an acetal, because it is too labile to be directly incorporated in the organozinc reagent. On hydrolysis of the acetal, the Michael adduct **162** is ready for the aldol condensation-cyclization cascade process, which leads to the chiral bicyclic enone framework **163**.

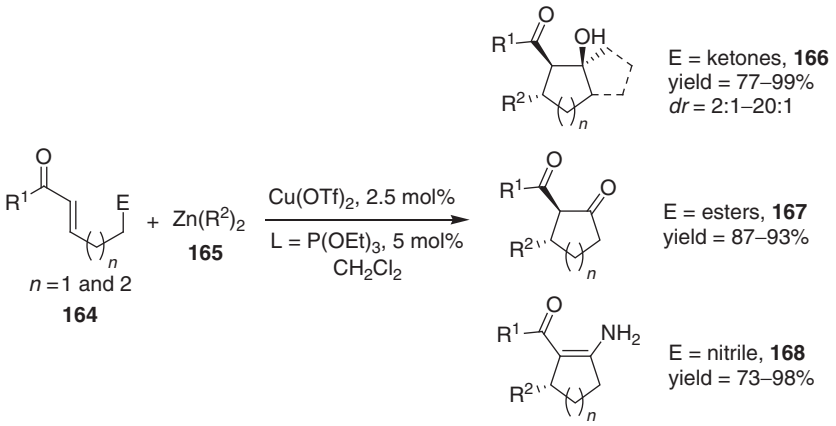


Scheme 32 Copper-catalyzed enantioselective annulations via Michael-aldol condensation reactions.

4.02.3.1.3 Integrated substrates and electrophiles

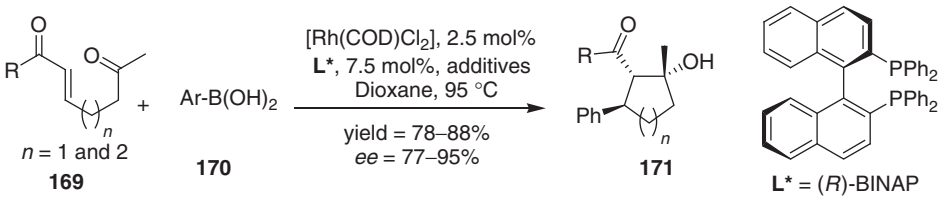
Krische and coworkers have demonstrated a copper-catalyzed tandem conjugate addition-electrophilic trapping protocol with ketones, esters, and nitriles as terminal electrophiles (Scheme 33).[29] The terminal electrophiles are intentionally tethered to enone moiety to achieve intramolecular electrophilic trapping. The $Cu(OTf)_2$ is indispensible for the catalytic system, as it activates the α,β-unsaturated ketone moiety in **164**. It is believed that the transmetallation from organozinc reagent to copper does not happen. An intermediate zinc-enolate is formed instead of copper-enolate after the initial conjugate addition. On the generation of the zinc-enolate, it is trapped by the tethered terminal electrophile to form cyclic product. If the electrophile is ketones, intramolecular aldol addition happens, and tertiary alcohols **166** are formed in good yield and with good diastereoselectivity. If the electrophile is

esters, intramolecular Dieckmann cyclization proceeds to give 1,3-diketones **167**. The electrophilic nitrile through a similar intramolecular Blaise cyclization affords enamines **168** with decent yield.



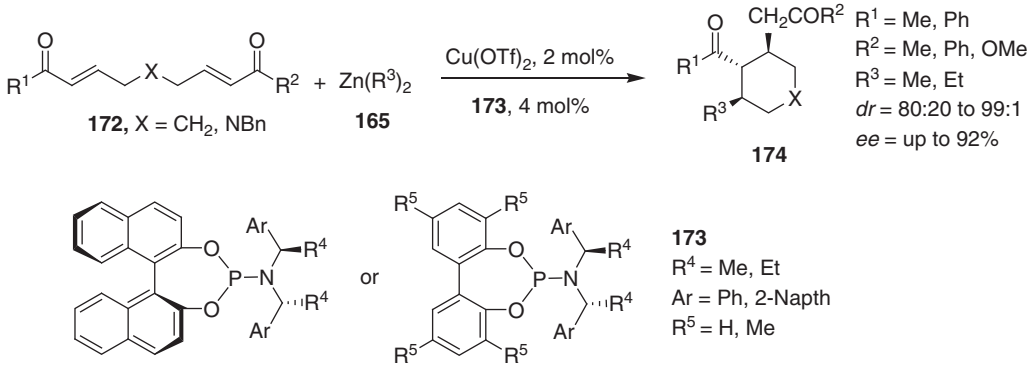
Scheme 33 Copper-catalyzed tandem conjugate addition-electrophilic trapping with various tethered terminal electrophiles.

The same group has also developed the asymmetric version of the cascade transformation (Scheme 34).[28] In this case, ketone moiety **169** is used as terminal electrophile, and arylboronic acids **170** as nucleophile. Rhodium complex with chiral ligand (*R*)-BINAP is assembled as a chiral catalyst. In this catalysis, transmetallation of the nucleophilic aryl moiety from boron to Rh(II) takes place to form rhodium-enolate intermediate, which is trapped by terminal electrophilic ketone. The attractive feature of this methodology resides in the ability to generate three contiguous stereogenic centers (**171**), including a quaternary center, in a single operation with efficient stereocontrol.



Scheme 34 Rhodium-catalyzed asymmetric tandem conjugate addition-aldol cyclization.

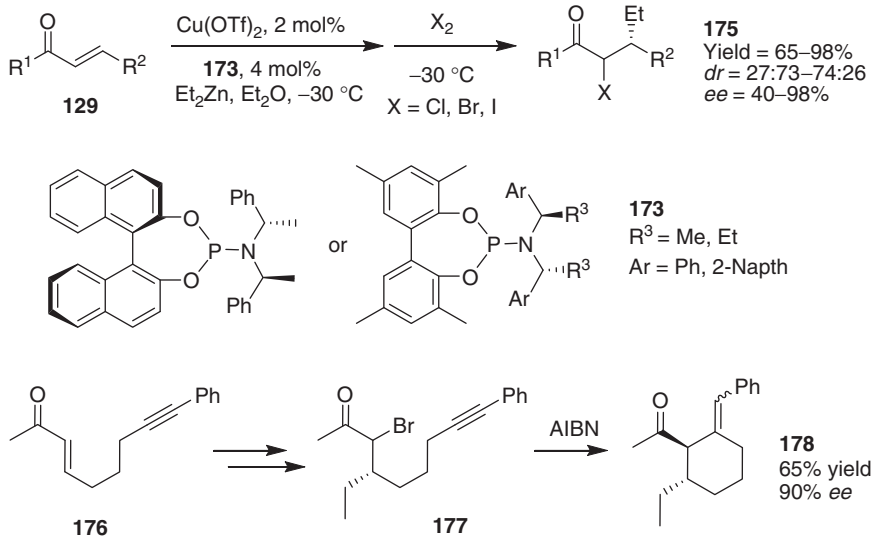
Alexakis and coworkers have discovered the enantioselective Michael–Michael cascade process using similar strategies (Scheme 35).[37] The copper-catalyzed conjugate addition of dialkylzinc **165** to bis-α,β-unsaturated carbonyl compound **172** is followed by the intramolecular trapping of the zinc-enolate in the presence of chiral phosphoramidite ligand **173**. The cyclic and heterocyclic compounds **174** with three contiguous chiral centers are formed with excellent stereoselectivities (up to 99:1) and enantioselectivities (up to 94% *ee*).



Scheme 35 Copper-catalyzed enantioselective double Michael cascade reactions.

4.02.3.2 Carbo-Nucleophiles with Halogenated Electrophiles

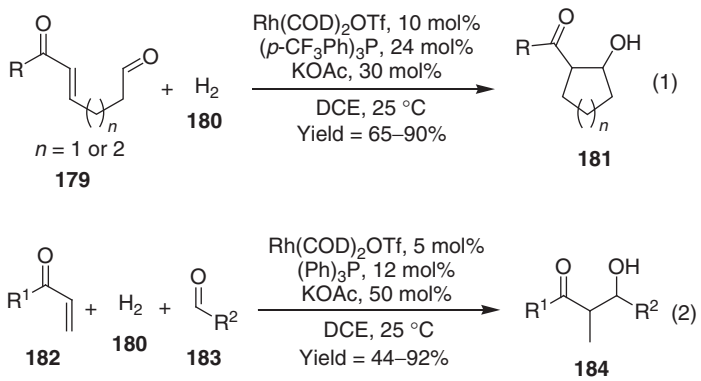
Alexakis and coworkers have developed an efficient one-pot reaction for the synthesis of chiral α-halo-β-alkyl ketones (Scheme 36).[38] The copper-catalyzed asymmetric conjugate addition-halogenation of enones is established, and the halogens are directly used as electropiles. As demonstrated in an example of further extension of the methodology, the halogenated chiral product **177** can be directly used in the radical cyclization to produce the cyclic compound **178** with 65% yield and 90% *ee*. The diastereoselectivity of the cascade sequence is not satisfactory, and there is room for further improvement.



Scheme 36 Copper-catalyzed asymmetric conjugate addition-bromination of enones.

4.02.3.3 Hydride-Nucleophiles with Carbo-Electrophiles

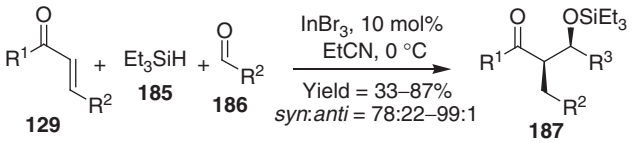
Krische and coworkers have reported a rhodium-catalyzed hydrogenative aldol cascade reaction using hydrogen gas (Scheme 37).[39] Both intramolecular cyclization and intermolecular condensation have been studied. Although the conjugate reduction of enones under hydrogenation conditions is well known, the situation that the *in situ* generated transition metal enolate uses H_2 is rare. The hydride-nucleophile is originated from rhodium-hydride complex after oxidative insertion of rhodium salt to H_2 (equation 1). The rhodium-enolate is subject to electrophilic trapping by appendant or exogenous aldehyde partners **179**, enabling catalytic C–C bond formation. As for the intermolecular reductive aldol cyclization, substrate scope is limited to β-unsubstituted enones **181** (equation 2).



Scheme 37 Rhodium-catalyzed hydrogenative aldol reaction of enones.

Baba and coworkers have demonstrated an In(III)-catalyzed diastereoselective reductive aldol reaction using triethyl silyl hydride **185** as reductant (Scheme 38).[40] The *in situ* generated indium hydride serves as the nucleophile for reductive conjugate addition to various enone substrates **129**. The intermediate indium-enolate is trapped by the external electrophilic aldehydes **186**. Because of the strong affinity of oxygen and silicon, the aldol adducts tend to associate with triethyl silyl moiety to produce final

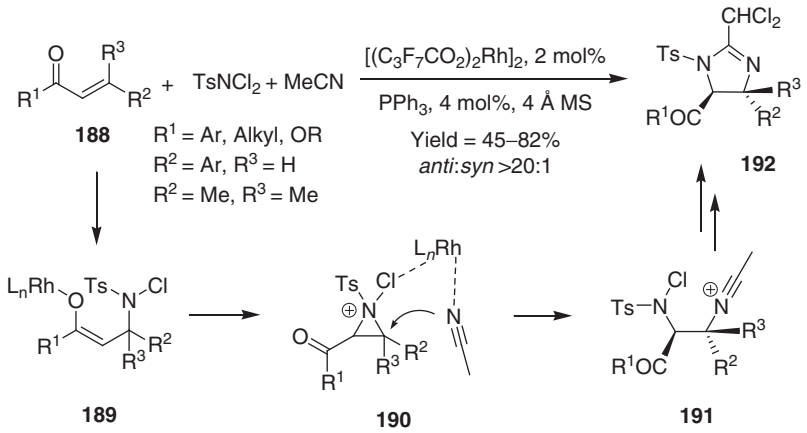
product silyl aldolates **187**. The indium-enolates are believed to react with electrophilic aldehydes **186** via a Zimmerman–Traxler six-membered cyclic transition state to afford favored *syn*-silyl aldolatez **187**. The use of triethyl silyl hydride **185** is convenient and clean, because it can be easily removed by evaporation after the reaction.



Scheme 38 Indium-catalyzed diastereoselective reductive aldol reaction.

4.02.3.4 Aza-Nucleophiles with Aza-Electrophiles

Li and coworkers have developed the novel electrophilic diamination reaction toward electron-deficient alkenes (Scheme 39).[40] Both α,β-unsaturated ketones and esters **188** can be used as substrates. The *N*-tosyl-*N*-chloroaziridinium intermediate **190** is believed to generate via aza-Michael addition tandem electrophilic cyclization. After further transformations, an interesting chlorinated cyclic diamination product **192** is received in good yield and good-to-excellent diastereoselectivity.



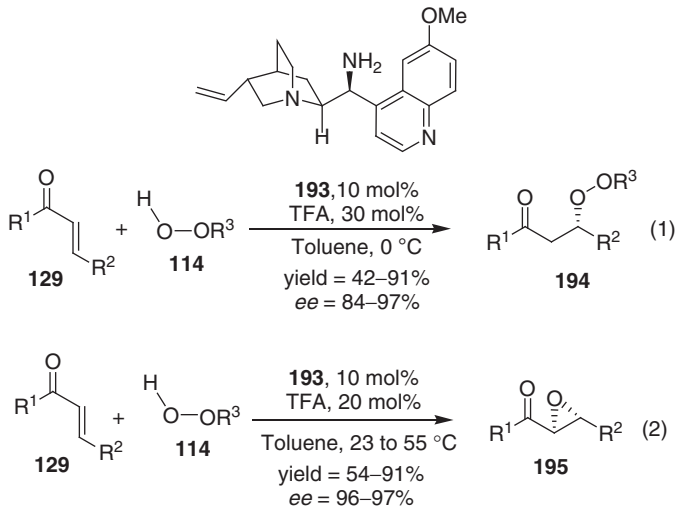
Scheme 39 Electrophilic diamination reaction of alkenes.

4.02.3.5 Oxa-Nucleophiles with Oxa-Electrophiles (Epoxidation)

Peroxides can be considered as an integrated oxa-nucleophile and oxa-electrophile. Asymmetric variants of the epoxidation reaction of α,β-unsaturated ketones with both chiral Lewis acids and organocatalysts have been reported. Deng and coworkers have developed highly enantioselective catalytic peroxidation and epoxidation methodologies using the same catalytic system (Scheme 40).[41] The epoxides **195** are formed via a two-step mechanism: nucleophilic addition of the peroxide to enones followed by an intramolecular electrophilic trapping of the resulting enolates that break the weak peroxide bond (equation 2). If the process of intramolecular trapping of the enolate intermediate is overwhelmed by protonation of the enolate, the epoxidation pathway will be converted into a peroxidation pathway (equation 1). In such a circumstance, the cascade process of epoxidation will be truncated into Michael addition reaction, and the Michael adduct peroxides **194** will be received as the major product (equation 1). Both peroxidation and epoxidation products are observed in initial exploration, and it is discovered that the peroxide/epoxide ratio inversely correlated with the reaction temperature. By increasing the reaction temperature from 0 °C to room temperature or 55 °C, the epoxidation products **195** are identified as the major product instead of the peroxidation products **194**.

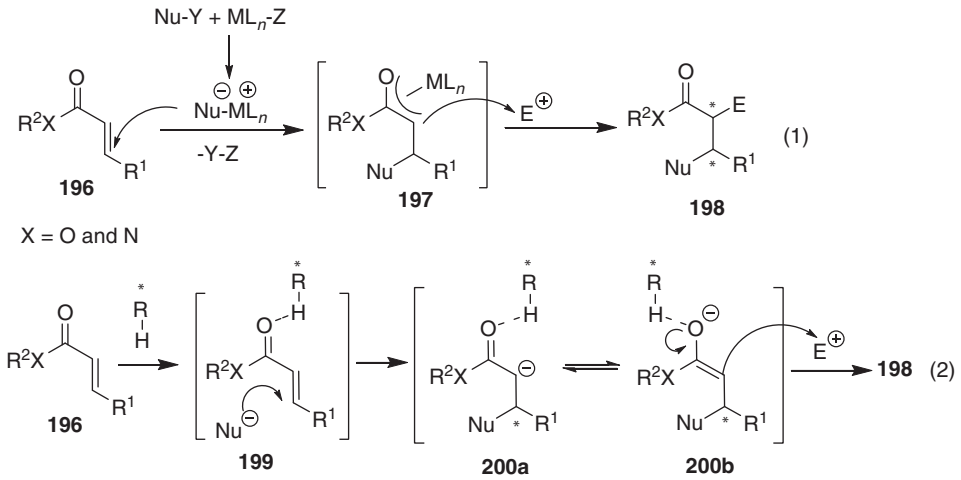
4.02.4 α,β-Unsaturated Esters and Amides

Comparing with aldehydes and ketones, esters or amides **196** are considered as weaker electronic withdrawing groups (Scheme 41). Accordingly, stronger nucleophiles or higher active catalytic systems are often used. Lewis acids play a major role in substrate activation via an enolate formation (equation 1), whereas the use of strong covalent bonded activated organocatalyst is



Scheme 40 Catalytic enantioselective peroxidation and epoxidation of enones.

difficult to be implemented with esters or amides. As a result, a noncovalent organocatalyst can be introduced alternatively in activation. Hydrogen bonding (equation 2), Brønsted acid, and phase transfer catalysts have been used. As described in equation 2, one or more hydrogen bonds can form between the carbonyl oxygen of a substrate and acidic proton of the catalyst, which renders the unsaturated system more electron-deficient.



Scheme 41 Lewis acids and small organic molecules-catalyzed conjugate addition-electrophilic couplings of α,β-unsaturated esters or amides (* indicates stereogenic centers potentially produced in these processes).

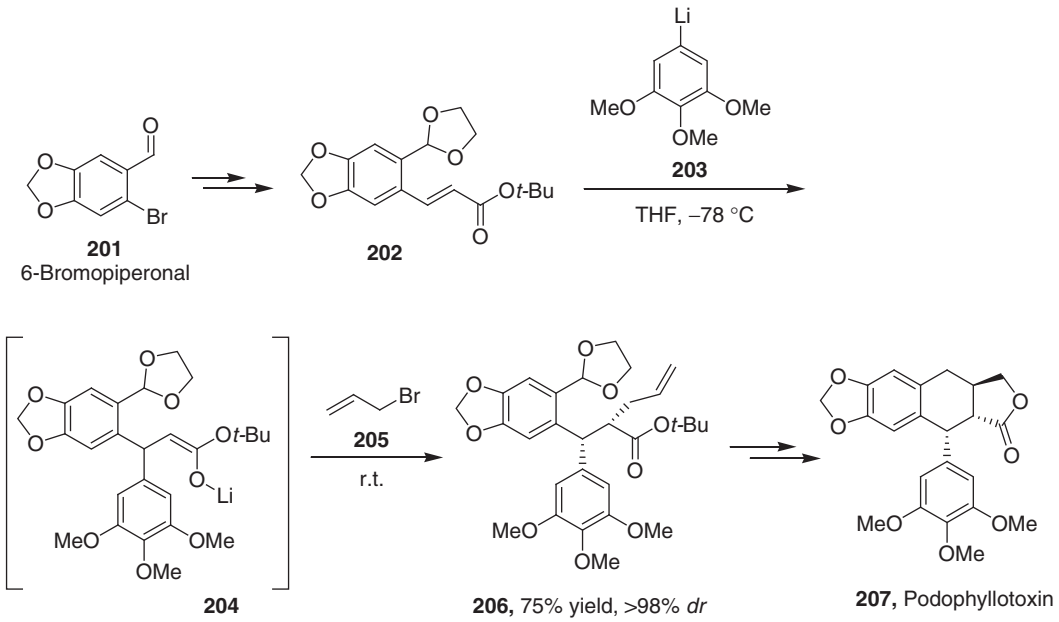
4.02.4.1 Carbo-Nucleophiles with Carbo-Electrophiles

4.02.4.1.1 Discrete nucleophiles and electrophiles

Zhang and coworkers have developed a highly practical, efficient, and stereoselective strategy for the total synthesis of podophyllotoxin **207** (Scheme 42).[42] The notable feature of this synthetic strategy is the use of the conjugate addition of organolithium reagent **203** tandem electrophilic alkylation cascade to ensure the key C1–C2 stereochemistry, which is crucial for the synthesis. Discrete nucleophile **203** and electrophile **205** are used together with α,β-unsaturated ester **202** as substrate. The stereoselectivity is controlled by lithium enolate intermediate **204**. The convenient route leads to podophyllotoxin **207** in only 12 steps with as high as 29% overall yield.

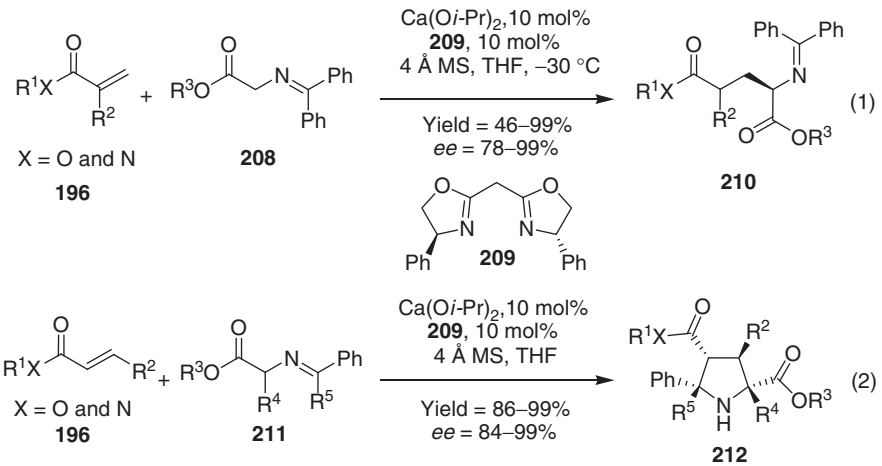
4.02.4.1.2 Integrated nucleophiles and electrophiles

To efficiently activate α,β-unsaturated amides and esters, Kobayashi and coworkers have developed novel Ca-Box catalysts **209** prepared from calcium alkoxides and methene bridged Box ligands (Scheme 43).[43] By selectively using branched or linear



Scheme 42 Synthesis of podophyllotoxin based on conjugate addition-alkylation cascade.

unsaturated carbonyl compounds **196** as Michael acceptor, the *in situ* generated chiral calcium complexes could effectively promote two types of catalytic asymmetric additions: Michael addition reactions (equation 1) and formal [3+2] cycloaddition reactions (equation 2). At temperature as low as −30 °C, the acrylate esters and amides **196** could react with glycine derivatives **208** to afford the desired Michael products **210** in high yields with high enantioselectivities. Using the same chiral calcium catalytic system **210** at higher temperature or for longer reaction time, linear α,β-unsaturated amides and esters **196** were allowed to react with more general α-amino acid derivatives **211** to produce pyrrolidine derivatives **212** via a cascade process of conjugate addition intramolecular electrophilic trapping. Although the possibility of a concerted [3+2] cycloaddition pathway could not be completely ruled out, the cascade mechanism of nucleophilic addition-electrophilic coupling is believed to be more plausible in this specific circumstance.

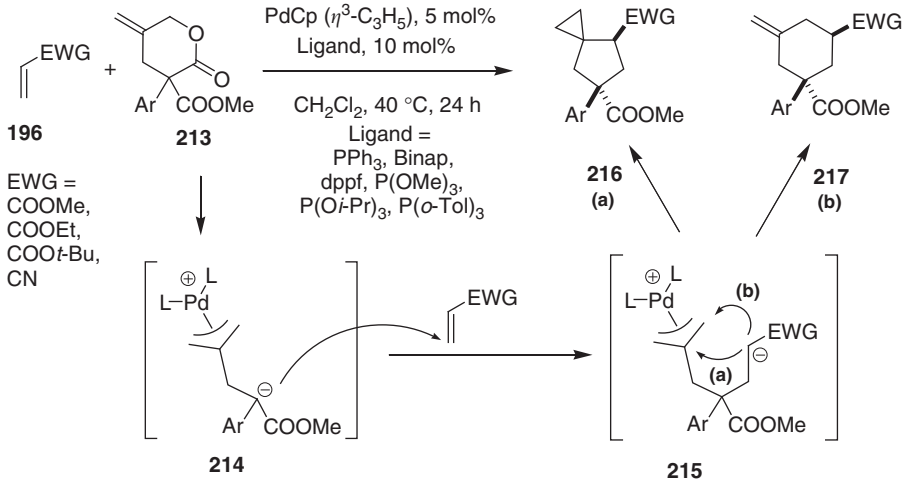


Scheme 43 Catalytic asymmetric conjugate addition and cascade reactions of α-amino acid derivatives with α,β-unsaturated esters and amides.

4.02.4.1.3 In situ *generated bifunctional intermediates*

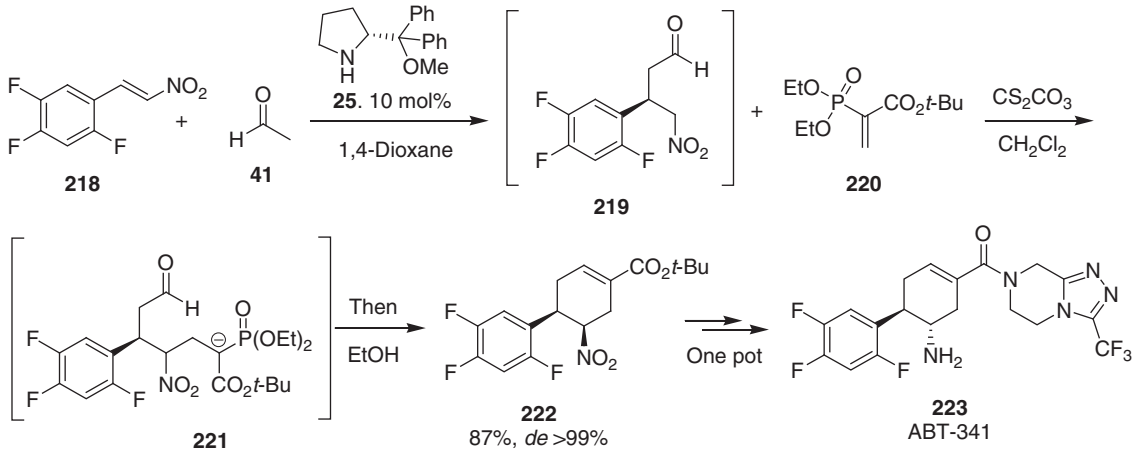
Shintani, Hayashi, and coworkers have developed a palladium-catalyzed intermolecular cycloaddition of γ-methylidene-δ-valerolactones with electron-deficient olefins to assemble spiro[2.4]-heptanes **216** and formal [4+2] cycloadducts **217** (Scheme 44).[44] After oxidative addition of palladium, followed by decarboxylation, the cyclic allyl ester **213** is transformed into 1,4-zwitterionic species **214**, which is a bifunctional intermediate containing both nucleophilic and electrophilic moieties. The initial

intermolecular conjugate addition leads to another zwitterionic intermediate **215**, which is ready for a ring-closure process. If the anionic carbon attacks the central carbon of the cationic π-allylpalladium moiety (route a), the spiro[2,4]heptanes **216** is received after reductive elimination of a palladacyclobutane intermediate. If it attacks the terminal carbon of the π-allylpalladium moiety (route b), the formal [4+2] cycloadduct **217** is generated. The regioselectivity is proposed to be controlled by ligand size. It is believed that small phosphine and phosphate ligands favor the central attack, and bukly phosphine ligands lead to terminal attack.



Scheme 44 Ligand-dependent palladium-catalyzed intermolecular cycloaddition.

An efficient, enantioselective total synthesis of ABT-341 is accomplished by Hayashi and coworkers in a single one-pot reaction (Scheme 45).[45] The reaction is initiated by the organocatalytic conjugate addition of acetaldehyde **41** to nitroolefin **218**. The Michael adduct **219** is not isolated, and participates in the Michael/Horner–Wadsworth–Emmons cascade that follows as a bifunctional intermediate to produce the cyclohexene **222** in 87% yield. The cyclohexene **222** is directly submitted to continuous one-pot operations without isolation and purification. The DPP4-selective inhibitor ABT-341 **223** is constructed in the fashion of six-step one-pot sequence with excellent overall yield of 63%.

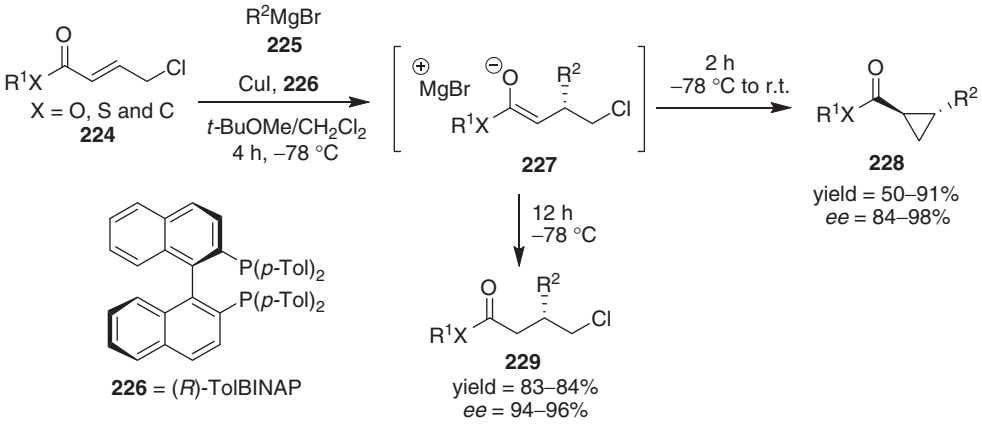


Scheme 45 The Michael/Horner–Wadsworth–Emmons cascade in the one-pot synthesis of ABT-341.

4.02.4.1.4 Integrated substrates and electrophiles

Feringa, Minnaard, and coworkers have illustrated a copper-catalyzed enantioselective cyclopropanation protocol (Scheme 46).[46] An *in situ* generated Cu-TolBINAP complex catalyzed the unusual conjugate addition of Grignard reagents **225** to various 4-chloro-α,β-unsaturated esters, thoesters, and ketones **224**. The key intermediates **227** lead to 4-chloro-3-alkyl-substituted carbonyl compounds **229** in up to 84% yield and 96% *ee* on protonation at low temperature. If the temperature is gradually elevated to room temperature within 2 h following the conjugate addition, with the help of the tethered chloride leaving group, the

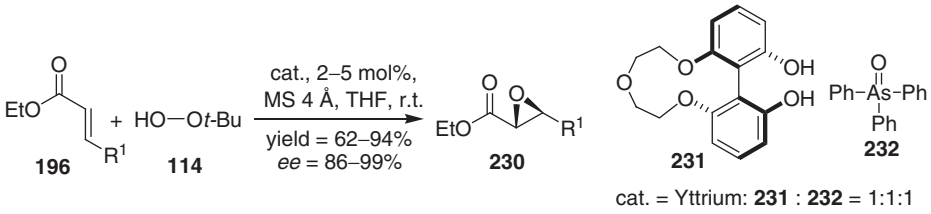
intramolecular electrophilic trapping of the enolate occurs instead to yield *trans*-1-alkyl-2-substituted cyclopropanes **228** in up to 92% yield and 98% *ee*.



Scheme 46 Copper-catalyzed enantioselective synthesis of *trans*-1-alkyl-2-substituted cyclopropanes.

4.02.4.2 Oxa-Nucleophiles with Oxa-Electrophiles (Epoxidation)

Shibasaki and coworkers have developed a catalytic asymmetric epoxidation reaction of α,β-unsaturated esters **196** triggered by conjugate addition of *tert*-butyl hydrogen peroxide **114** by a yttrium-biphenyldiol complex (Scheme 47).[47] After screening of various rare earth metals, yttrium is found to provide satisfactory catalytic efficacy. The success of the reaction also depends on the properties of the diethylene ether-tethered biphenyldiol ligand **231**, which can dramatically boost the reactivity of the yttrium-based metal complex.

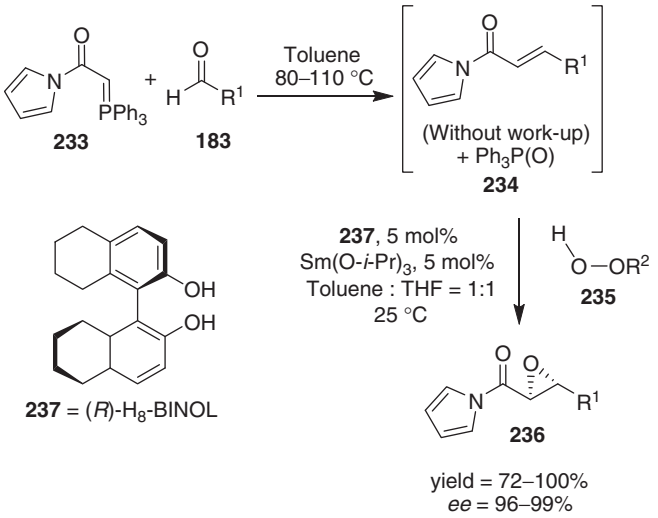


Scheme 47 Catalytic asymmetric epoxidation of α,β-unsaturated esters by yttrium-biphenyldiol complex.

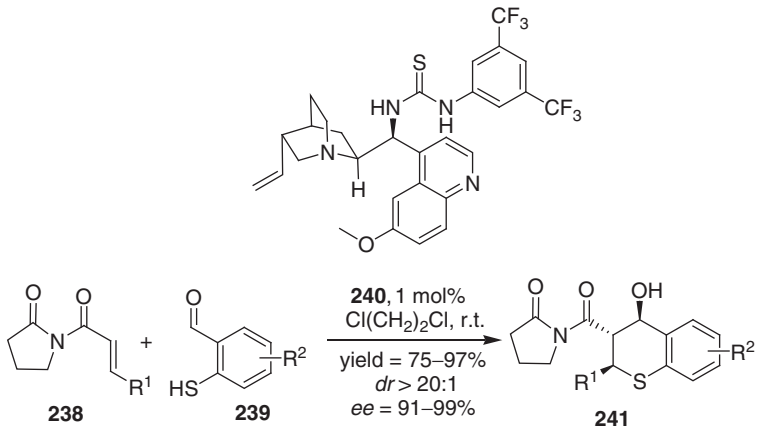
The same group has also demonstrated the utility of α,β-unsaturated *N*-acylpyrroles **234** as monodentate ester surrogate in the catalytic asymmetric epoxidation reaction (Scheme 48).[48] The α,β-unsaturated *N*-acylpyrroles with various function groups are directly synthesized by the Wittig reaction using ylide **233** and aldehydes **183**. The resulting olefination products **234** serve as monodentate substrate for the enantioselective epoxidation without work-up and purification. The usage of samarium-based chiral complex can successfully reduce the catalyst loading to as little as 0.02 mol%. Good yields (72–100% from aldehydes **183**) and excellent *ee* (96–99%) are achieved with broad substrate generality.

4.02.4.3 Sulfur-Nucleophiles with Carbo-Electrophiles

Wang and coworkers have developed a highly enantioselective and diastereoselective organocatalytic thio-Michael-aldol cascade process for the preparation of chiral thiochromanes (Scheme 49).[49] The one-pot process is promoted by a cinchona alkaloid-derived thiourea **241** with catalyst loading of as low as 1 mol%. Closely mimicking the action mode of enzyme catalysis, the effective bifunctional organocatalyst **241** contains two modules, which synergistically activate both the Michael donor and acceptor. The thiourea moiety interacts with the α,β-unsaturated oxazolidinones **238** via two hydrogen bonds. The tertiary amine of cinchona alkaloid serves as a general base to enhance the nucleophilicity of the 2-mercaptobenzaldehyde **239**. The multi-substituted chiral thiochromanes bearing three contiguous stereogenic centers are produced rapidly (1–10 h) in high yields (75–97%) and with excellent enantiomeric excess (91–99%) and diastereomeric ratios (>20:1).



Scheme 48 Sequential Wittig-catalytic asymmetric epoxidation reaction with aldehydes.



Scheme 49 Organocatalytic tandem enantioselective thio-Michael-aldol reaction.

4.02.5 Nitroolefins

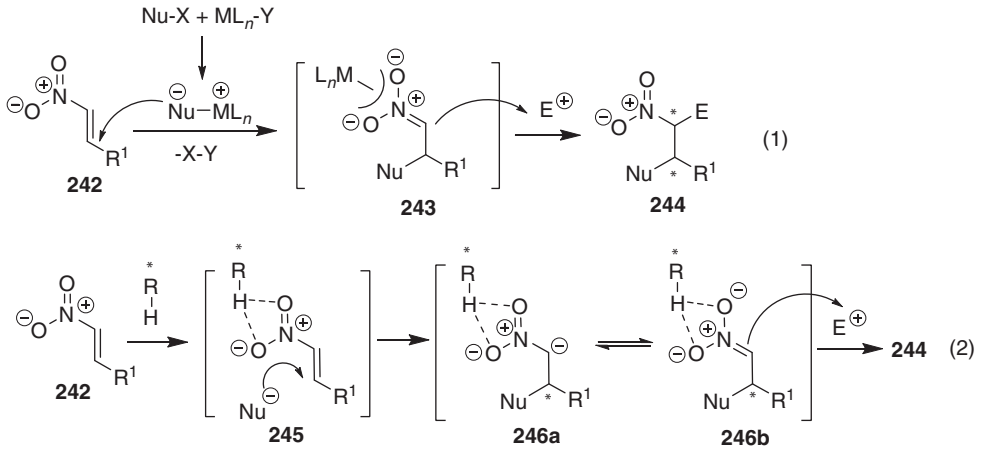
Compared with α,β-unsaturated esters and amides, nitroolefins **242** share similar features concerning activation modes (Scheme 50). Because they are not able to form a covalent bond with secondary amines, noncovalent bond organocatalysts represented by weak hydrogen bond catalysts are usually employed for the activation of nitroolefins. Lewis acids are also good candidates for the cascade process of nucleophilic addition-electrophilic coupling. Because the nitro functional group can provide two oxa-binding sites, the activation of more active nitroolefins is relatively more effective than α,β-unsaturated esters and amides. As a result, in most of the cases, nitroolefins can participate in cascade sequences without any catalytic activation.

4.02.5.1 Carbo-Nucleophiles with Carbo-Electrophiles

4.02.5.1.1 Discrete nucleophiles and electrophiles

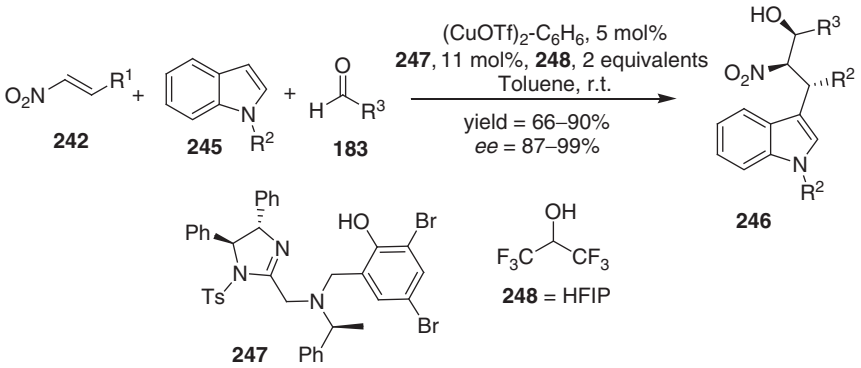
Arai and coworkers have developed a three-component cascade reaction of nitroolefins **242**, indoles **245**, and aldehydes **183** to construct chiral indole derivatives **247** with three contiguous stereocenters (Scheme 51).[50] The **247**-Cu(OAc)$_2$ complex is used to catalyze the enantioselective Henry reaction of nitroalkanes and aldehydes to give the 1,2-adduct with up to 95% *ee*. In this example, the **247**-CuOTf complex in the presence of **248** can also mediate the Friedel–Crafts reaction of indole with nitroalkenes. The electrophilic aldehyde **183** is treated with the **247**-Cu catalytic system, indole **245** as Michael donor and nitroolefin **242** as Michael acceptor, and the Michael adducts can be trapped to produce product **246** with up to 90% yield and 99% *ee*.

Hayashi and coworkers have developed an asymmetric one-pot synthesis of substituted tetrahydropyranols **245** and **246** with excellent diastereo- and enantio-selectivity through diphenylprolinol sily ether **25** mediated Michael reaction of aldehydes **41** and nitroolefins **242**, followed by a subsequent Henry and acetalization cascade (Scheme 52).[51] External electrophiles, such as ethyl



Scheme 50 Lewis acids and small organic molecules-catalyzed conjugate addition-electrophilic trapping of nitroolefins (* indicates stereogenic centers potentially produced in these processes).

glyoxylate **244** or aldehydes **183**, are added consecutively to trap the γ-nitroaldehyde intermediates **243** via Henry reaction. If a moderate organic base (triethyl amine) and nonpolar solvent (toluene) are used in the substep, kinetically controlled products **245** are obtained with nitro group in the axial position. When strong base (DBU) and polar solvent (acetonitrile) are used, thermodynamically governed products **246** are formed with nitro moiety in the equatorial position. When the kinetic product is treated with DBU, isomerization into stable thermodynamic product occurs.



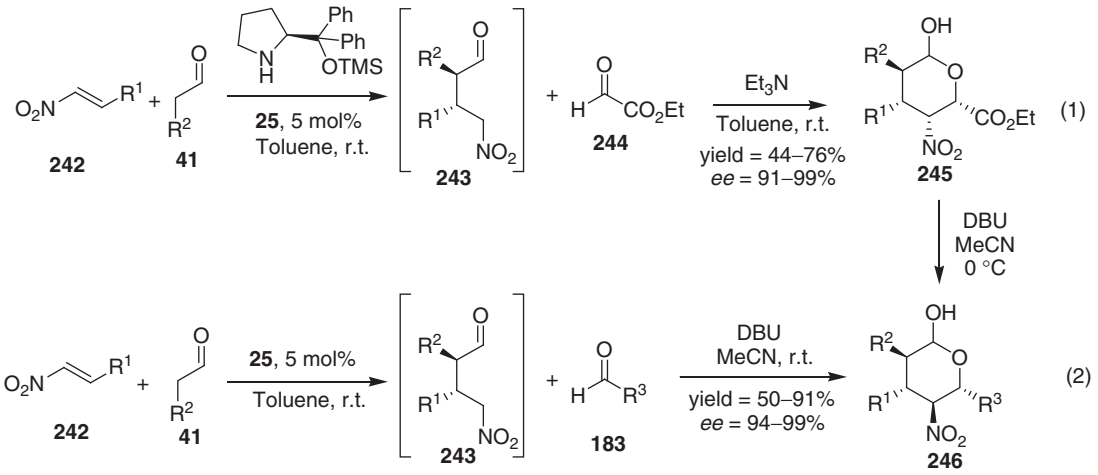
Scheme 51 Copper-catalyzed asymmetric Friedel–Crafts–Henry cascade reactions.

The rapid, one-pot enantioselective total synthesis of (–)-oseltamivir **253** has been achieved by Hayashi and coworkers using the organocatalytic asymmetric cascade strategy (Scheme 53).[52] The process is initiated by Michael addition of aldehyde **247** to nitroolefin **248**, catalyzed by diphenylprolinol sily ether **25** via an enamine activation mode. The Michael adduct **249** is trapped by electrophilic vinylphosphonate **250** via Henry-type Michael addition. The resulting intermediate **251** is ready for Horner–Wadsworth–Emmons reaction to form the cyclohexene core **252** under basic condition. The Tamiflu **253** is isolated in the overall yield of 57% after the follow-up transformations.

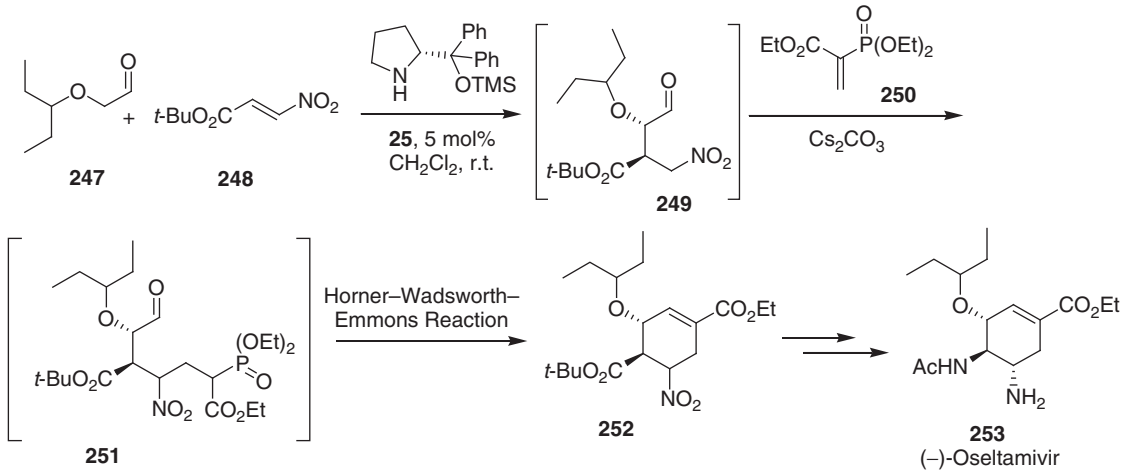
4.02.5.1.2 Integrated nucleophiles and electrophiles

Melchiorre and coworkers have demonstrated a chiral primary amine-catalyzed double Michael cascade reaction of nitroalkenes **242** with α,β-unsaturated ketones **254** (Scheme 54).[53] The enone **254** with an enolizable α-carbon integrates both nucleophilic and electrophilic moieties. Supported by the unique stereochemical outcome of the products **256**, the cinchona alkaloid-derived primary amines **255** effectively activate acyclic enones **254** to form enamines and selectively direct the active species toward a stepwise double Michael addition involving nitroolefines then enones sequence instead of a pericyclic [4+2] cycloaddition pathway.

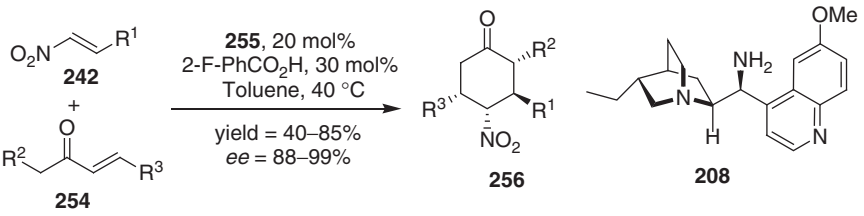
Yan and coworkers have illustrated a convenient and efficient method for the asymmetric construction of nitrocyclopropanes via the organocatalytic conjugate addition of dimethyl bromomalonate to nitroalkenes and the consequent intramolecular cyclopropanation (Scheme 55).[54] The bromomalonate **37** represents the integrity of nucleophilic moiety as well as electrophilic



Scheme 52 Organocatalytic asymmetric Michael–Henry acetalization cascade reactions.



Scheme 53 The synthesis of Tamiflu using organocatalytic asymmetric cascade strategy.

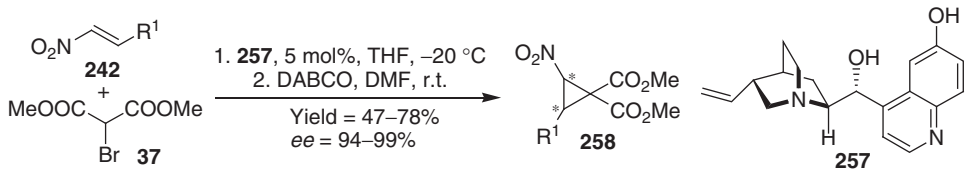


Scheme 54 Chiral primary amine-catalyzed double Michael cascade reaction.

moiety for the cascade process. With the help of the 6′-demethyl quinine catalyst **257** that directly activate nitroalkene **242** via intermolecular hydrogen bonds, excellent enantioselectivities, diastereoselectivities, and good chemical yields were achieved.

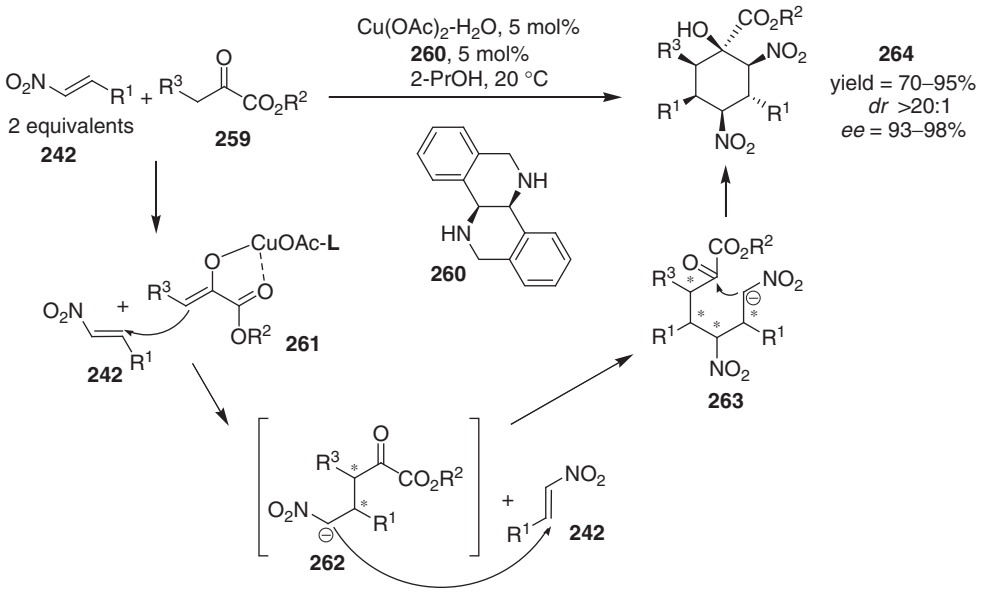
4.02.5.1.3 In situ *generated bifunctional intermediates*

Huang and colleagues have disclosed a highly enantioselective and diastereoselective copper-catalyzed asymmetric formal [2+2+2] annulation between *α*-ketoesters **259** and nitroalkenes **242** (Scheme 56).[55] The *in situ* generated chiral Lewis acid catalyst activates the *α*-ketoesters **259** to produce the intermediate copper-enolates **261**, which then attack nitroolefins **242** by a conjugate addition to yield carbanion intermediates **262**. The intermediate **262** is trapped by the second nitroalkenes **242** to produce carbanion intermediates **263**. Mechanistically, the first nitroalkene molecule participates in the first cascade sequence of



Scheme 55 Organocatalytic asymmetric cyclopropanation of nitroalkenes (* indicates stereogenic centers potentially produced in these processes).

nucleophilic addition, then tandem electrophilic coupling. The intermediates **263** are subject to an intramolecular Henry reaction to give rise to the highly functionalized cyclohexane carboxylate **264**. The second nitroalkene substrate engages in the second cascade sequence of nucleophilic addition and electrophilic trapping. Starting from extremely simple reactants, the cascade reaction assembles six contiguous stereocenters in one step with excellent enantioselectivity and complete diastereoselectivity.



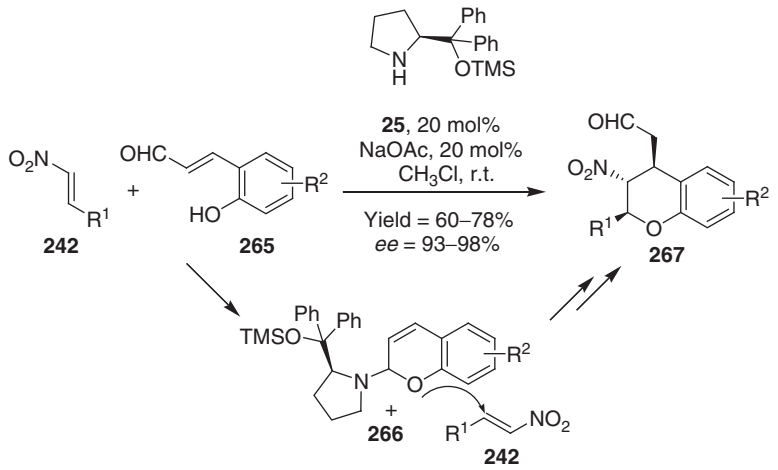
Scheme 56 Copper-catalyzed asymmetric formal [2+2+2] annulation reactions (* indicates stereogenic centers potentially produced in these processes).

4.02.5.2 Oxa-Nucleophiles with Carbo-Electrophiles

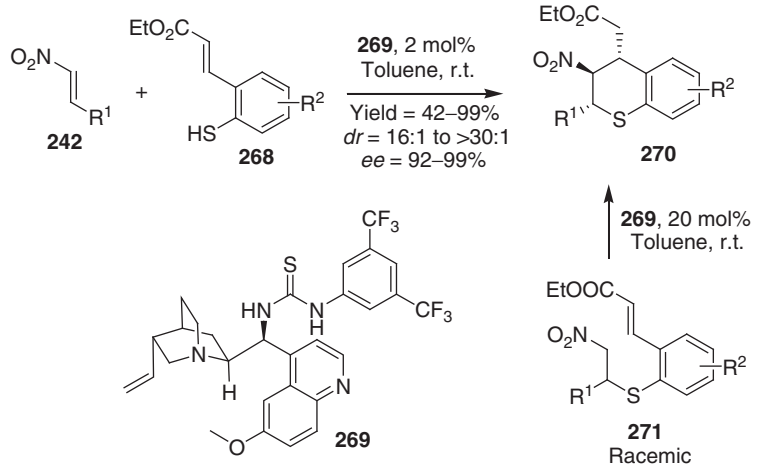
Wang and coworkers have demonstrated an organocatalytic oxa-Michael–Michael cascade strategy for the facile construction functionalized chiral chromans (Scheme 57).[56] The integrity **265** consists of nucleophilic hydroxyl group and electrophilic Michael acceptor, and can associate with TMS protected diphenylprolinol catalyst **25** to form aminal **266**, which serves as a nucleophile, rather than a free phenol hydroxyl group for the Michael addition. The oxa-Michael adduct is trapped by the tethered enal moiety to carry out an intramolecular conjugate addition. The cascade process produces a multisubstituted chiral chromans **267** with three stereogenic centers in a simple and practical approach.

4.02.5.3 Sulfur-Nucleophiles with Carbo-Electrophiles

As it has been demonstrated previously, conjugate addition with thiol as Michael donor is usually reversible due to the weak S–C bond. However, the weakness can be overcome by trapping the Michael adduct with foreign electrophile, and the reversibility can also be utilized in dynamic transformation for stereocontrol. Wang and coworkers have developed an organocatalytic stereoselective Michael–Michael cascade reaction through dynamic kinetic resolution (Scheme 58).[57] The cinchona alkaloid-derived thiourea catalyst **269** synergistically activates both the nitroolefin **242** through hydrogen bonds and the nucleophile via deprotonation, and brings the two reactants to close vicinity. The Michael adduct **270** of nitroolefin and thiophenol can undergo retro-Michael process in the presence of the bifunctional catalyst, and such a process is confirmed by treatment of racemic adduct **271** under the standard reaction conditions. The DKR process is believed to take place in the second Michael addition step, and the process can overcome the racemization of the initial Michael adduct **271**.



Scheme 57 Organocatalytic oxa-Michael–Michael cascade reaction of nitroolefin.



Scheme 58 Hydrogen bond-mediated Michael–Michael cascade process through dynamic kinetic resolution.

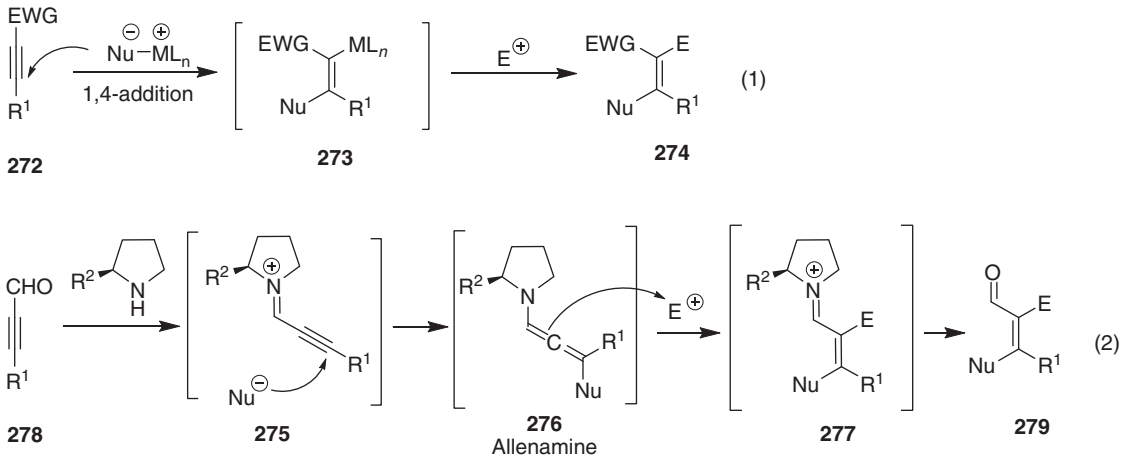
4.02.6 Alkynes

Alkynes are also able to participate in the cascade processes of nucleophilic addition-electrophilic coupling without prerequisite activation of the triple bond via electronic withdrawing group attached to the sp-hybridized carbons. In such a circumstance, strong nucleophilic organometallic species are usually used to initiate the cascade, and the tandem difunctionalization reactions proceed through carbometallation to produce a vinylic organometal intermediate **273** (Scheme 59, equation 1). The organometallic species possess the nature of carbanion, and can be trapped by an electrophile to generate bifunctional product **274**. However, to the knowledge of the authors, a Lewis acid-catalyzed protocol for enantioselective construction of chiral frameworks has not been reported.

In another perspective, organocatalysts are good promoters, able to mediate the cascade sequences of nucleophilic addition-electrophilic coupling under mild reaction conditions to fabricate delicate frameworks and achieve stereoselective control (Scheme 59, equation 2). The widely used chiral secondary amines have been utilized to activate acetylenic aldehydes **278**. The Michael addition of a nucleophile to acetylenic iminium **275** produces a chiral allenamine **276**. The trapping of the allenamine by electrophile delivers tetra-substituted alkene **279**. Because the intermediates of both the conjugate addition and the electrophilic trapping are chiral motifs, stereogenic centers form during the asymmetric catalysis.

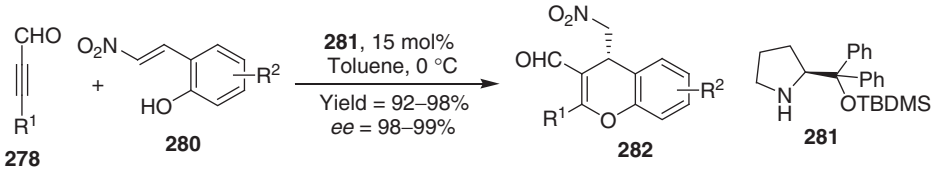
4.02.6.1 Oxa-Nucleophiles with Carbo-Electrophiles

Wang and coworkers have developed an asymmetric oxa-Michael–Michael reaction involving an unprecedented chiral iminium allenamine-mediated cascade sequence (Scheme 60).[58] The nucleophilic phenol moiety and electrophilic nitroolefin moiety are



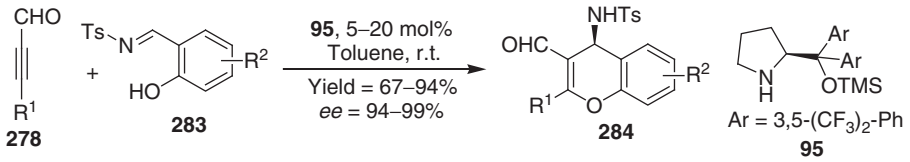
Scheme 59 Lewis acids and secondary amines-catalyzed nucleophilic addition-electrophilic coupling of alkyne substrates (* indicates stereogenic centers potentially produced in these processes).

incorporated into one reactant **280** to achieve one-pot synthesis of biologically significant chiral 4*H*-chromenes **282** in high yields and with excellent enantioselectivities by organocatalyst **281**. The stereogenic center is originated from the nitroolefin moiety, and the stereoselectivity is obtained from intramolecular asymmetric trapping of the chiral allenamine intermediate.



Scheme 60 Chiral secondary amine promoted enantioselective cascade oxa-Michael–Michael reaction of acetylenic aldehydes.

Ruano and coworkers have presented an enantioselective oxa-Michael–aza-Baylis-Hillman (or oxa-Michael–Mannich) cascade reaction with acetylenic aldehydes and tosylimines leading to optically active 4-amino-4*H*-chromenes **284** (Scheme 61).[59] The strategy is almost same as the previous example. The tosylimine moiety is used as electrophile instead of nitroolefin, and the stereogenic center is formed via asymmetric trapping of chiral allenamine intermediate.



Scheme 61 Organocatalytic asymmetric oxa-Michael–aza-Baylis-Hillman tandem reaction.

4.02.7 Outlook

As shown in this chapter, significant achievements have been made in the field of nucelophilic addition-electrophilic coupling reactions. In addition to traditional orgnometallics as catalysts in promoting these processes, organocatalysis has emerged as a new complementary strategy and has been demonstrated as a powerful tool in the facile construction of complex molecular architectures. Furthermore, it is noteworthy that a number of unprecedented enantioselective catalytic nucelophilic addition-electrophilic coupling cascade processes have been developed in organocatalysis, which may be otherwise difficult to realize with chiral Lewis acids. These processes afford efficient approaches to synthetically valuable complex building blocks in organic synthesis. It is expected that more new catalytic nucelophilic addition-electrophilic coupling cascade reactions are continuing to be developed. Although complex molecular architectures can be created from these cascade processes, their applications in natural

product synthesis are very limited. Furthermore, expanding scope beyond Lewis acids and organocatalysts catalysis is an important direction. This relies on the development of new activation modes. Moreover, combining organometallic and organo-catalysis in the design of new catalytic nucelophilic addition-electrophilic coupling cascades represents an active area to come.[60]

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4.03 Organocatalytic Asymmetric Nucleophilic Addition to Electron-Deficient Alkenes

JL Vicario, E Reyes, L Carrillo, and U Uria, Facultad de Ciencia y Tecnología, Bizkaia, Spain

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Glossary

Brønsted acid/base catalysis Organocatalysis based on the activation of one (or more) substrate(s) through a Brønsted acid or a Brønsted base.

Covalent catalysis Organocatalysis based on the generation of intermediates in which the catalyst is bound covalently to the substrate(s)/product(s) through a reversible chemical reaction.

Enamine activation Organocatalysis based on the generation of an enamine intermediate which will act as a nucleophile in a subsequent organic reaction.

H-bonding catalysis Organocatalysis based on the activation of one (or more) substrate(s) through the formation of a hydrogen bond network with the catalyst (typically urea, thiourea, squaramide, etc.).

Iminium activation Organocatalysis based on the generation of an iminium species, which will act as an electrophile or dienophile in a subsequent organic reaction (typically Michael reactions and cycloadditions).

Organocatalysis Acceleration of chemical reactions through the addition of a substoichiometric quantity of a low molecular weight organic compound (organocatalyst), which does not contain a metal atom on its structure (and acts in the primary catalytic cycle).

Phase transfer catalysis (PTC) Catalysis based on the activation of one (or more) substrate(s), which will react in a biphasic system (typically an organic/aqueous system).

4.03.1 Introduction

Asymmetric organocatalysis, which is defined as the ability of small chiral organic molecules that do not contain metal atoms in their structure to catalyze certain chemical transformations in a stereoselective way, has become a fundamental tool in modern organic synthesis for the preparation of enantiopure compounds.[1] The last few years have witnessed an impressive growth of this field of research, reaching a level of sophistication and efficiency that has made many authors establish that organocatalysis constitutes one of the three cornerstones that hold the field of asymmetric catalysis, together with metal catalysis and the use of enzymes. The main reason for the very rapid development of this field relies mainly on the operational and economical advantages typically associated with this methodology, together with the fact that organocatalysts are environmentally friendly, robust, and very often commercially available reagents. As a result, many research groups have engaged in the development of organocatalytic alternatives to transformations that are typically carried out using transition-metal catalysis, and this has also contributed to the advance of chemical sciences with the discovery of some important new concepts.

Among all organic reactions for which the corresponding organocatalytic variant has been developed, the conjugate addition reaction has been without any doubt the most studied transformation, with plenty of examples described in the recent literature.[2] The rich profile of this reaction, with a wide variety of potential compounds amenable to participate as electron-deficient alkene electrophile (also referred to as Michael acceptor) or as nucleophile (the Michael donor) undoubtedly contributes to this situation. Moreover, the intrinsic nature of the conjugate addition reaction, in which a carbanionic nucleophilic intermediate is generated after the initial addition reaction, makes this transformation an exceptional ground field for the implementation of cascade or domino reactions. This is an additional element of interest that has triggered the intensive research and application of organocatalytic methodologies to the conjugate addition reaction.[3] In this chapter, we intend to survey the methodologies reported until 2011 for carrying out enantioselective conjugate additions using organocatalysis as the methodological approach to achieve stereocontrol. However, we have only included those methodologies in which the conjugate addition product is quenched in the reaction medium by the addition of a proton to the nucleophile intermediate that is formed after the addition step and, therefore, those examples in which the generation of this intermediate has also been used for implementing cascade processes have not been covered herein.

Organocatalytic methodologies have been classified according to the corresponding operating mechanism in each case and, in this context, two different classifications have been disclosed: one of them is focused on the acid/base reactivity of the catalyst and the other on the type of interaction involved in the activation of the reagents. In this sense, List[4] initially proposed that organocatalysts should be classified according to their acid/base character, thereby establishing four different categories: Lewis bases, Brønsted bases, Brønsted acids, and Lewis acids. However, perhaps the most widely used and accepted classification of organocatalytic methodologies makes use of the nature of the catalyst–substrate interaction leading to a very general classification of organocatalytic methodologies as covalent or noncovalent catalysis. Figure 1 shows the different activation mechanisms associated with most of the examples reported in the literature for carrying out enantioselective conjugate additions. Aminocatalysis is the archetypical example of covalent catalysis, in which the activation of the substrates participating in the Michael reaction is achieved by the reversible formation of an enamine (activation of the Michael donor)[5] or an iminium ion (activation of the Michael acceptor).[6] *N*-heterocyclic carbenes represent the other important class of covalent catalysts, which participate in the activation of the pronucleophile by the formation of an addition intermediate known as the Breslow intermediate.[7] The very close substrate to catalyst interaction attained with these catalysts allows a very effective influence of the catalyst in the stereochemical outcome of the reaction, however, it makes catalyst turnover much more difficult, which typically results in rather long reaction times and the need for higher catalyst loadings. Alternatively, within the group of noncovalent organocatalysts, the substrate–catalyst interaction relies typically on the cooperative participation of weaker interactions and this is the case of those reactions involving the formation of catalyst–substrate complexes through hydrogen bonds (H-bonding catalysis),[8] chiral ion pairs (phase-transfer catalysis[9] and Brønsted base catalysis),[10] or other types of supramolecular aggregation complexes.

This chapter has been organized according to the type of Michael donor participating in the reaction and, within each case, disclosing the different examples according to the mechanism operating in the activation of the reagents by the organocatalyst during the conjugate addition process, taking into account that almost all the methodologies reported till date fall into one of the five categories addressed in Figure 1. It should also be pointed out that, in several cases, multifunctional catalysts have been developed in the sense that they incorporate different elements in their structure that allow simultaneous activation of the two reagents that participate in the conjugate addition reaction, which also results in the fact that different mechanisms can operate. In those cases, and whenever possible, we have classified the methodology into the category which was crucial for catalytic activity.

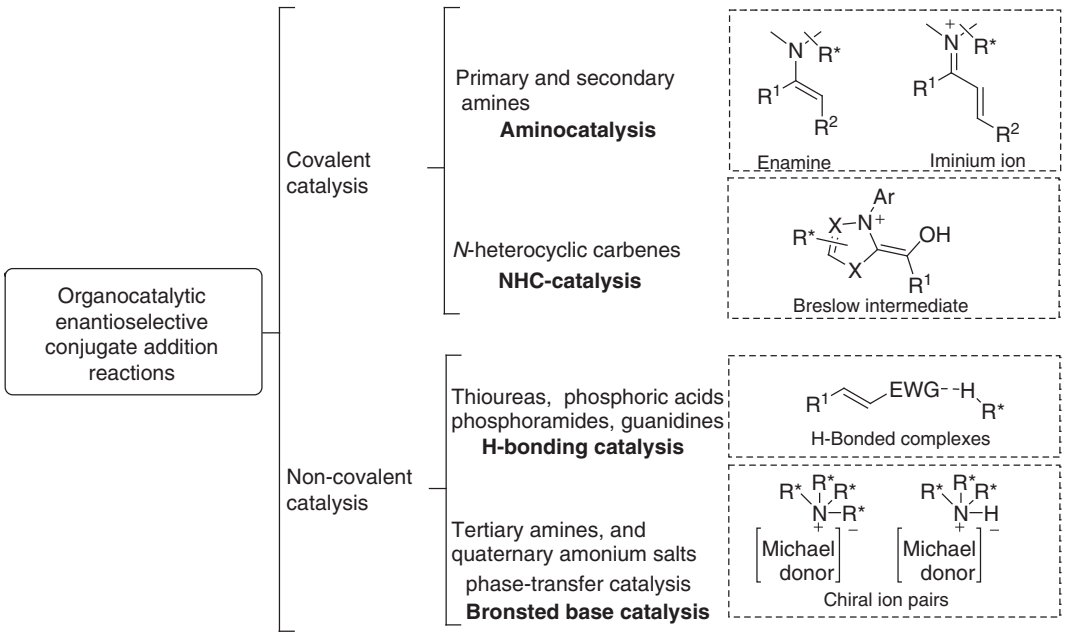


Figure 1 Classification of organocatalytic conjugate addition reactions according to the substrate–catalyst interaction.

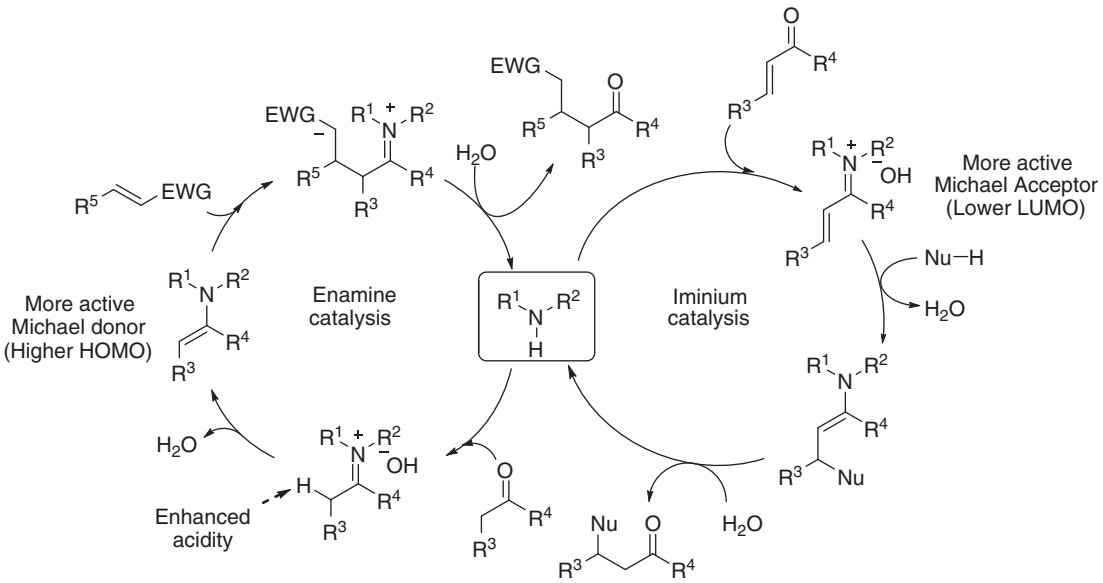
4.03.1.1 General Activation Mechanisms in Organocatalytic Conjugate Addition Reactions[11]

4.03.1.1.1 Aminocatalysis

Primary or secondary amines are highly versatile catalysts for promoting conjugate additions because these can be used for the activation of both the reagents participating in the reaction. They are able to activate enolizable aldehydes or ketones toward their participation as nucleophiles in a Michael reaction via reversible formation of an enamine intermediate species or, alternatively, they can also activate an α,β-unsaturated aldehyde or ketone through the reversible formation of an iminium ion, allowing its participation as the Michael acceptor partner (Scheme 1).

The catalytic cycle involved in the enamine activation mechanism consists of the initial enamine formation step by condensation reaction between the catalyst and the Michael donor pronucleophile followed by the conjugate addition step, leading to the formation of an iminium ion intermediate which, on hydrolysis, releases the product and the amine catalyst. The initial condensation step is crucial for the activation of the Michael donor, leading to the formation of an enamine intermediate in which a significant raising of the energy of its HOMO results in the formation of an active nucleophile. On the other hand, the foundations behind the iminium activation concept rely on the fact that the formation of the iminium ion intermediate results in the lowering of the LUMO of the Michael acceptor, therefore becoming activated for the conjugate addition reaction, which now takes place much faster than the possible background uncatalyzed reaction. After the conjugate addition step takes place, an enamine intermediate is formed, which undergoes hydrolysis for catalyst turnover. Remarkably, the participation of this enamine-type intermediate in this catalytic cycle opens the way for a domino process to occur, if an appropriate electrophile is included in the reaction which is able to react inter- or intramolecularly with this enamine intermediate.

In addition, the catalyst must exert its stereochemical influence by controlling the approach of the Michael acceptor or donor by one of the two diastereotopic faces of the corresponding intermediate (enamine or iminium ion, respectively). This stereodiscrimination can be carried out by steric bias or, alternatively, by introducing a convenient stereodirecting element at the catalyst like, for example, a substituent able to engage in H-bond interactions with a basic point of the incoming reagent. In all cases, controlling the geometry of the formed enamine or iminium intermediate is an important issue that has to be considered for reaching a high level of stereocontrol. Condensation of a primary or secondary amine with an aldehyde or a ketone can lead to the formation of two *Z* or *E* diastereoisomers in varying proportions depending on the structure of the reagents and these, in addition, interconvert between each other through different dynamic processes. Moreover, these key reactive enamine or iminium ion

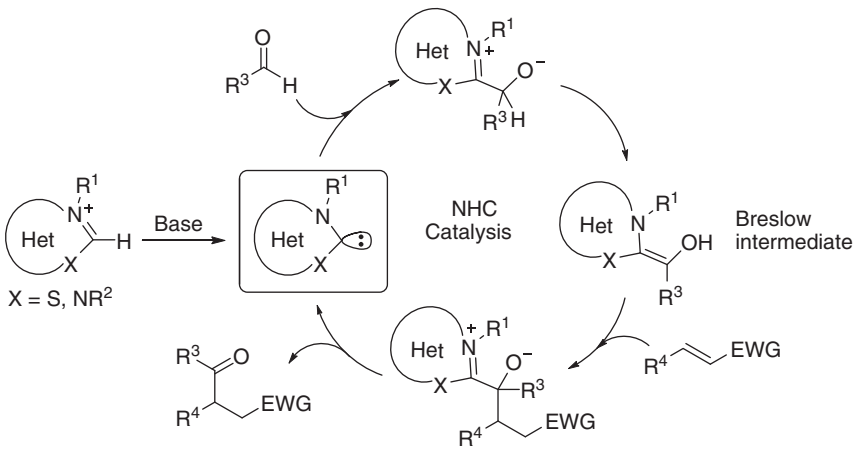


Scheme 1 Catalytic cycle for aminocatalytic Michael reactions.

intermediates present a high conformational freedom and the different geometries in which these intermediates can appear during the conjugate addition step can lead to the formation of the new stereocenters in different configurations. For this reason, stereocontrol in the reaction has to be controlled by incorporating the required structural elements into the amine catalyst in order to assure that these intermediates participate in the catalytic cycle through a well-defined geometry.

4.03.1.1.2 NHC catalysis

N-Heterocyclic carbenes are able to activate aldehydes toward their participation as nucleophiles in Michael reactions, therefore resulting in a typical example of an umpolung process. This reaction, which is known as the Stetter reaction, was reported initially in a nonstereoselective version in 1975,[12] although the corresponding enantioselective approaches have been reported quite recently. The mechanism operating in *N*-heterocyclic carbene-mediated conjugate addition reactions involves the addition of the carbene catalyst (which is typically generated *in situ* by deprotonation of the corresponding heterocyclic salt precursor) to the aldehyde reagent, generating a nucleophilic intermediate which is also known as the Breslow intermediate. Next, this intermediate undergoes 1,4 addition with the Michael acceptor and a final elimination step releases the product and allows the turnover of the catalyst (Scheme 2).



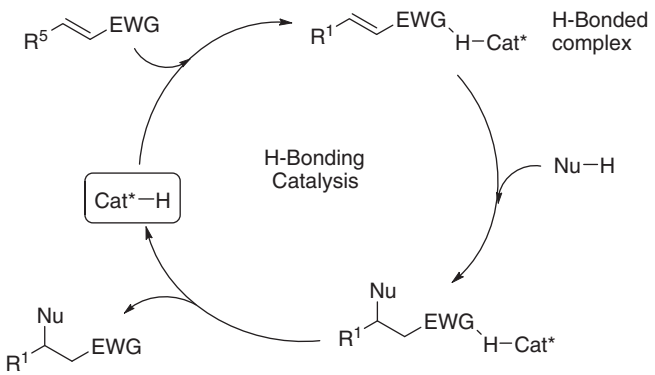
Scheme 2 Catalytic cycle for the Stetter reaction.

The general principle applied to the development of enantioselective NHC-catalyzed conjugate addition reactions relies on the use of catalysts incorporating a central heterocyclic azolium salt core for the generation of the reactive carbene moiety, together with lateral side chains incorporating the chiral information required to achieve enantiocontrol. In this context, the most effective

catalysts usually rely on conformationally rigid structures which reduce the degrees of conformational freedom and also try to locate the chiral information in the closest proximity to the reaction center.

4.03.1.1.3 H-Bonding catalysis

Brønsted acidic compounds are able to activate electrophiles such as the Michael acceptors by the formation of a hydrogen-bonded structure, which releases electronic density from the electrophile resulting in a significant decrease in energy of its LUMO and therefore becoming activated toward the conjugate addition reaction. This mechanism of action closely resembles the one operating in the activation of electrophiles by metal-centered Lewis acid catalysts, in which the same LUMO-lowering effect happens as a consequence of the formation of a dative bond between the metal and a Lewis basic site at the electrophile. In this sense, organocatalysts operating through these type of interactions are usually compounds that incorporate multiple hydrogen donors for increasing the binding affinities between the catalyst and the substrate and also with a focus on providing a much better organization in the transition state, which also leads to improved stereoselectivities. Nevertheless, the identification of chiral phosphoric acids and phosphoramides as rather strong organic Bronsted acids has also led to their application as catalysts in several examples of conjugate addition reactions in which these catalysts only contribute to the activation of the Michael acceptor through a single H-bonding event (Scheme 3).



Scheme 3 Catalytic cycle for conjugate addition reactions via H-bonding catalysis.

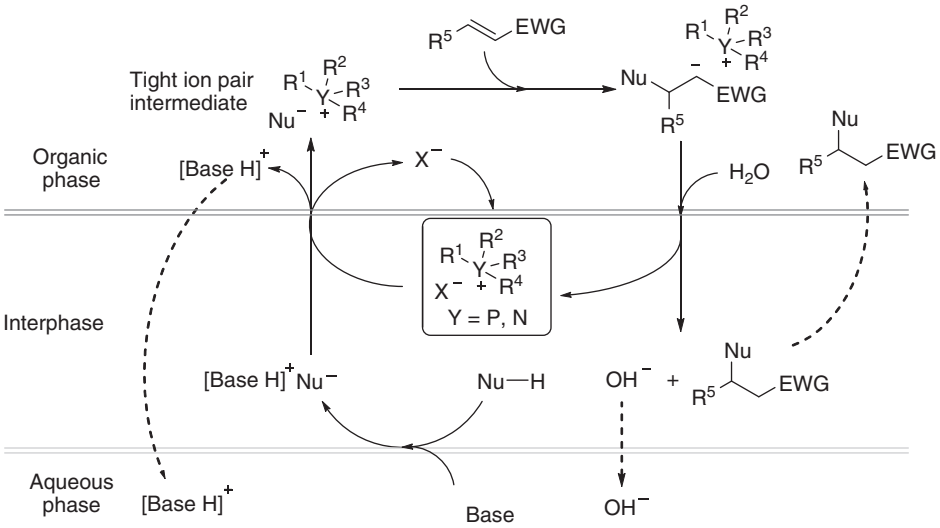
It should be stressed that several other cases of organocatalytic enantioselective conjugate addition reactions exist in which hydrogen bonding events also play an important role for achieving high levels of stereocontrol, although in these cases, these H-bonding interactions can be considered as secondary interactions that mostly participate by contributing to the preorganization of the reagents in the transition state.

4.03.1.1.4 Catalysis through chiral ion pair formation

Quaternary ammonium or phosphonium salts are able to catalyze the conjugate addition reaction between a Michael donor reagent and an electrophilic olefin, which are located in different immiscible phases through the formation of an ion-paired intermediate (Phase Transfer Catalysis or PTC). The mechanism of the reaction is depicted in Scheme 4 and starts with the activation of the pronucleophile by deprotonation with a Brønsted base at the interface between the organic and the aqueous layers, to give the corresponding anion which next undergoes ion exchange with the catalyst, leading to the formation of a lipophilic chiral nucleophile, able to penetrate into the organic phase where the conjugate addition reaction takes place. As the conjugate addition product still retains its anionic character, it remains linked to the catalyst at the organic phase and subsequently undergoes protonation by water, releasing the conjugate addition product and the catalyst, the former being transferred to the organic layer and the latter returning to the interface ready to participate in a subsequent catalytic cycle. It is important for the success of the reaction that the initial ion-exchange process occurs rapidly enough to avoid the competitive background conjugate addition reaction between the deprotonated pronucleophile and the Michael acceptor in the absence of the chiral catalyst. Moreover, a close interaction between the nucleophile anion and the cationic catalyst is required in the transition state in order to guarantee an effective chirality transfer during the formation of the stereocenters.

It should also be pointed out that not all the reactions proceeding under PTC conditions are carried out in an aqueous/organic biphasic mixture, but very often, an inorganic base is used as the Brønsted base for the initial deprotonation of the pronucleophile, which is incorporated as a solid reagent to a solution of Michael donor, Michael acceptor, and the catalyst in an organic solvent. In these cases, all the processes involved in the transference of reagents between the two phases have to occur in the interface of the solid reagent, which is referred to in the literature as solid–liquid phase-transfer catalysis conditions.

Alternatively, a number of different conjugate addition reactions can also be catalyzed by chiral Brønsted bases, which participate in the reaction by activating the pronucleophile through deprotonation, leading to the formation of an anionic species which should remain tightly bound to the corresponding chiral countercation. Therefore, the overall principle underlying this activation mode is essentially the same as that operating in PTC catalysis, although in this case the reaction proceeds in a



Scheme 4 The mechanism operating in conjugate addition reactions via PTC catalysis.

homogeneous environment. Moreover, it should be pointed out that this type of nucleophile activation by deprotonation using chiral Brønsted bases is very often found in many examples of enantioselective conjugate addition reactions as part of a bifunctional catalyst. In these cases, this type of activation is considered as a secondary interaction which assists the formation of a more well-defined transition state as it also happened with the previously mentioned H-bonding interactions, regardless of the fact that the presence of such a Brønsted basic site on a bifunctional catalyst can also play a fundamental role in the success of the reaction.

4.03.2 The Michael Reaction

The catalytic enantioselective conjugate addition of resonance-stabilized carbon nucleophiles (an enolate or related species) is possibly one of the most effective approaches for the preparation of chiral nonracemic 1,5-dicarbonyl compounds. The synthetic versatility of this reaction relies mainly on the broad spectrum of possible reagents amenable to participate as carbon-centered Michael donors and also on the wide variety of electron-deficient olefins that can be used as Michael acceptors, as it has been demonstrated by the large number of examples in which it has been applied as a key strategic transformation in total synthesis. In particular, this reaction has played an active role as a test ground for the application of almost all the previously described organocatalytic activation mechanisms, achieving in many cases an extraordinary level of success.

4.03.2.1 Enamine Catalysis

As previously shown in Section 4.03.1.1.1, several chiral primary and secondary amines have demonstrated their ability to catalyze the enantioselective Michael reaction of enolizable carbonyl compounds with electron-deficient olefins via the formation of an intermediate enamine species and therefore, the application of this methodology is strictly limited to the use of Michael donors capable of forming enamines (aldehydes or ketones). In addition, the rather low reactivity of these type of nucleophiles very often limits the application of this reaction to the use of activated Michael acceptors such as, for example, nitroalkenes or alkylidenemalonates. Importantly, the most attractive feature of this strategy compared with many of the related metal-catalyzed versions is that previous activation of the pronucleophile is avoided because it is the catalyst itself that activates the Michael donor reagent. This results in a higher atom efficiency of the process and also allows employing unmodified aldehydes as donor reagents, which are challenging substrates to be used as a source of the typical nucleophiles required in metal-catalyzed versions of this transformation (enolates or silyl enol ethers). Another advantage of the enamine activation strategy applied to the Michael reaction is the capacity to carry out the reaction under neutral conditions and also that the compatibility of all intermediates participating in the catalytic cycle toward the presence of moisture or oxygen opens up the possibility to carry out the reaction in open air and using bulk solvents.

4.03.2.1.1 Nitroalkenes as Michael acceptors

The Michael reaction of aldehydes and ketones with nitroalkenes can be regarded as one of the most studied transformations in which the enamine activation concept has been applied. This reaction furnishes highly functionalized adducts with remarkable potential in organic synthesis, due to the synthetic versatility of the nitro group and the presence of the carbonyl moiety from the donor reagent. The first attempts in this field were carried out in the proline-catalyzed Michael reaction of ketones with

nitrostyrene, which consisted of an initial proof of principle for the application of the enamine activation concept to Michael reactions.[13] In all these cases, the obtained yields and diastereoselectivities were remarkably high, although moderate enantioselectivities were obtained. Almost simultaneously the reaction between aldehydes and nitroalkenes catalyzed by a proline-based diamine was also reported, which proceeded with a much higher enantioselectivity.[14] After these pioneering reports, many different groups have engaged in the development of chiral secondary amine catalysts able to promote this reaction and, in this context, most of the initial fundamental studies have been directed to the use of cyclohexanone as a model substrate for the design and optimization of catalyst structure and reaction conditions. As can be seen from Figure 1, many different chiral secondary amines, mostly derived from proline, have been prepared and tested in the reaction with a variety of nitroalkene reagents with different degrees of success (Figure 2).[15–37]

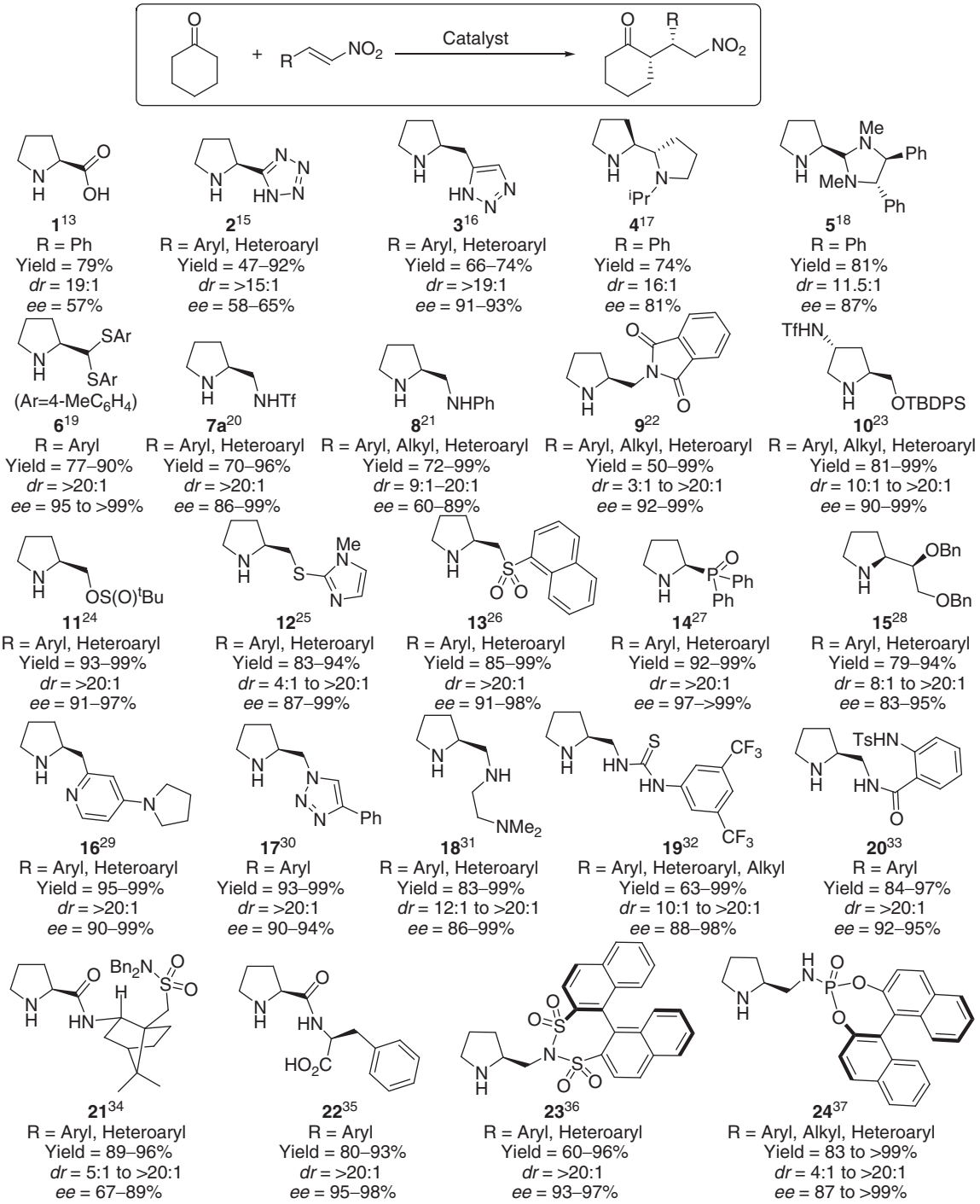
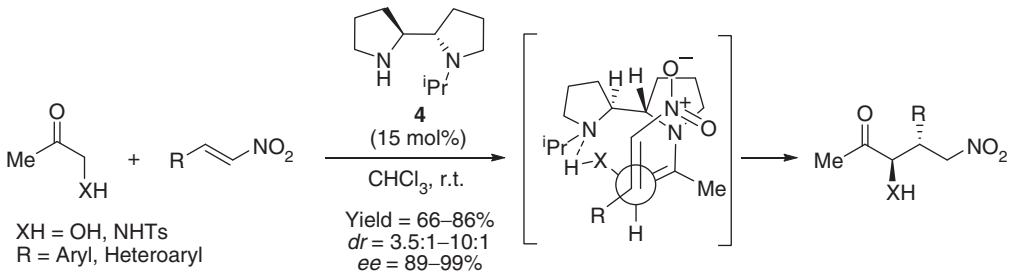


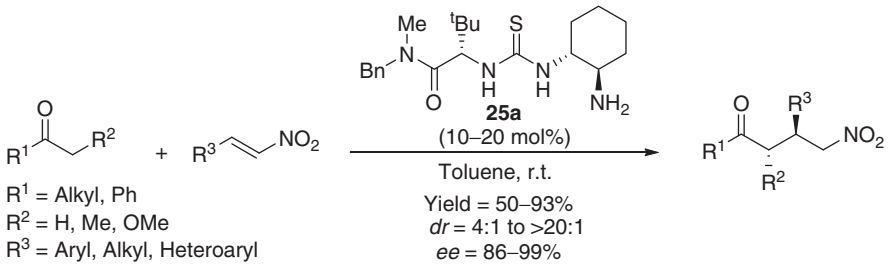
Figure 2 Chiral secondary amine catalysts employed in the Michael reaction of cyclohexanone with nitrostyrenes under enamine activation.

It should be pointed out that, in general, those systems which are efficient for cyclohexanone are also useful compounds to be used as catalysts with other symmetric ketones either cyclic (cyclopentanone, cycloheptanone, or substituted cyclohexanones and related six-membered heterocyclic compounds) or acyclic like acetone or 3-pentanone, even though the results are very often highly dependent on the size of the ring in the first case and/or the nature of the substituents in the second case.[38] The use of α-heterosubstituted ketones as Michael donors entails a situation which deserves special attention, because, in this case, the presence of the α-heteroatom can facilitate controlling the regioselectivity and the geometry in the generation of the enamine intermediate through secondary intramolecular H-bonding interactions. For example, catalyst **4** has been studied in the reaction of α-hydroxy- and α-amino ketones with nitroolefins explaining the high stereocontrol achieved in terms of the preferential formation of a *Z*-enamine assisted by intramolecular hydrogen bonding with the amine-containing side chain of the catalyst (Scheme 5).[39]



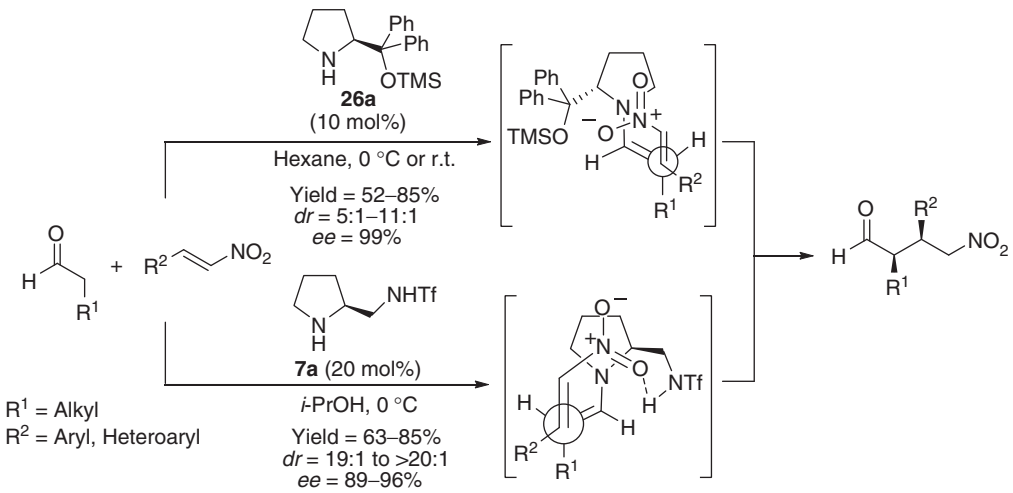
Scheme 5 Enantioselective Michael reaction of α-hydroxy- and α-aminoketones with nitroalkenes.

However, most of these catalysts that perform rather well in this model reaction, usually fail when employed with other more challenging acyclic ketones, in which the presence of substituents of different size and nature at both sides of the carbonyl group incorporates an additional regioselectivity issue that has to be controlled if a single compound is desired. Moreover, and with respect to stereocontrol, the presence of these two different substituents also entails a challenging situation in the sense that controlling the geometry of the enamine intermediate is also much more difficult than in those cases in which cyclic ketones were employed as Michael donors. A solution to this problem has been provided with the discovery that primary amines can operate as highly active and efficient aminocatalysts in several Michael transformations proceeding via enamine activation.[40] The condensation reaction between a ketone and a primary amine is sterically more feasible and, in addition, the geometry control on this intermediate is also easier because of the higher differences in steric bulk between the coplanar substituents across the conjugated N–C=C moiety. In fact, the literature examples indicate that primary amines are much more active catalysts for the Michael addition of both cyclic and acyclic ketones to nitroalkenes compared with the same reaction using a secondary amine catalyst like most of the proline-based derivatives already presented in Figure 2. Moreover, almost all the primary amine catalysts developed and employed in this reaction typically incorporate a second functionality at the catalyst structure, which is able to engage in H-bonding interactions with the nitroalkene acceptor, thereby leading to the formation of a well-ordered arrangement of reagents in the transition state. A particularly synergistic situation is found when chiral primary amines containing a thiourea moiety are used as catalysts due to the ability of thiourea to engage in highly stabilizing and selective interactions with the nitrocompounds through a double H-bonding network. Several catalysts of this type have been developed, but thiourea **25a** developed by Jacobsen has shown to be a particularly efficient one in terms of substrate scope, showing an excellent performance for a wide variety of differently substituted ketones and also behaving well when both *β*-aryl- and *β*-alkyl-substituted nitroalkenes were employed as electrophiles, the latter being considered as challenging Michael acceptors that usually provide rather poor results (Scheme 6).[41] Following a similar reaction design, other bifunctional chiral primary amine catalysts have been developed, which contain other functionalities different from the thiourea moiety that can also engage in effective H-bonding interactions with the nitroalkene Michael acceptor.[42]



Scheme 6 Enantioselective Michael reactions of ketones with nitroalkenes catalyzed by primary amine-thiourea catalyst **25a**.

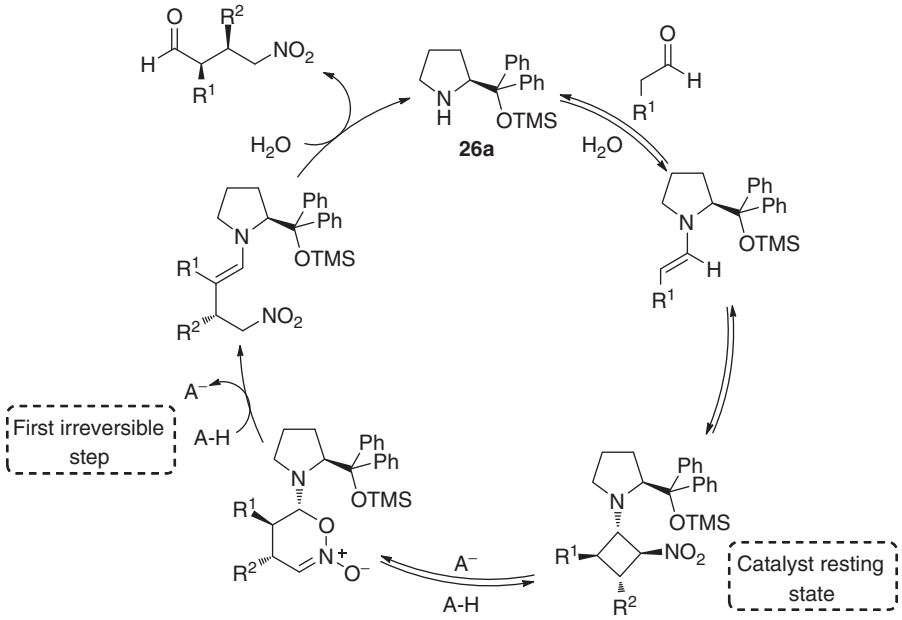
However, a great deal of the work in this area has been focused on the use of aldehydes as Michael donors, mainly because they behave much better than ketones in this reaction when chiral secondary amines are employed as organocatalysts due to their higher ability to condense with the catalyst to furnish the corresponding enamine intermediate. Moreover, in this case the geometry and conformation control on the enamine intermediate is much easier because of the large differences in size between the two substituents of the enamine moiety. Nevertheless, and despite this intensive research, *O*-TMS protected diarylprolinols such as **26a**[43] still remain the most effective catalysts in terms of yields, stereoselectivities, and also because of their performance when applied in target-oriented synthesis.[44] The key for the success of this type of diarylprolinol catalysts relies on the effect exerted by the very bulky 2-substituent at the pyrrolidine ring which, on one hand, allows a very efficient geometry control of the enamine intermediate, favoring the preferential formation of the *anti* conformer and on the other hand it exerts an excellent steric shielding of one of the two diastereotopic faces.[45] An alternative catalyst design consists of the introduction of stereodirecting elements able to establish secondary interactions with the Michael acceptor. Sulfonyldiamine **7a** also derived from proline is a good example of such a catalyst, which also performs very well in the reaction between aldehydes and nitroalkenes.[46] In this case, the key for the high stereocontrol furnished by this catalyst should be attributed to the formation of a rigid hydrogen-bonded transition state by interaction between the highly acidic NHTf moiety and the nitro group, which also determines one preferred reactive arrangement for the enamine intermediate (Scheme 7).



Scheme 7 Two very effecive chiral secondary amines for catalyzing the Michael reaction of aldehydes with nitroalkenes.

This reaction and, in particular, the **26a**-catalyzed Michael reaction of propanal with nitrostyrene, has been the subject of a concise study directed toward the identification of the exact mechanisms operating in this transformation and also toward an understanding of the true source of the enantioselection exerted by the catalyst.[47] These studies have resulted in the identification of several new intermediates participating in the catalytic cycle (Scheme 8). In particular, the reaction was found to proceed initially through the formation of a stable cyclobutane intermediate, which afterwards undergoes a base-promoted ring-opening process delivering a 1,2-oxazine intermediate (also detected), which on protonation/ring opening renders a third stable enamine intermediate and the latter releases the product and the free amine catalyst after a final hydrolysis. Kinetic experiments determined that the protonation of this 1,2-oxazine intermediate results to be the first irreversible step of the overall catalytic cycle, all the previous intermediates being in equilibrium between each other and also that the stable cyclobutane intermediate detected appears to be in a resting state in the catalytic cycle, rather than being a parasitic species that sequesters the catalyst. This means that all the intermediates that precede this cyclobutane species become equilibrated, which indicates that the stereodetermining step might not be the one in which the C–C bond formation takes place, as it had been pointed out in the initial models furnished to explain the stereocontrol such as those indicated in Scheme 7, which are based on the assumption that stereochemistry is installed in the step in which the conjugate addition of the enamine intermediate to the nitroalkene takes place. This new proposal establishes a more complex situation in which enantioselectivity would depend on the combination of two separate factors: one kinetic component given by the relative rate constants for the first irreversible protonation step (the protonation of the 1,2-oxazine intermediate) and a second one which becomes determined by the relative equilibrium constants for all the equilibrating diastereoisomeric mixtures of all intermediates which are formed before this first irreversible step.

Intensive research in this field has led to the design of a wide number of different types of catalysts, generally consisting of a central pyrrolidine scaffold containing different types of substituents at the 2-position, and most of them also easily accessible from the natural amino acid L-proline.[48–58] Figure 3 shows different chiral pyrrolidines and related derivatives that have been employed as catalysts in the Michael reaction of aldehydes with nitroalkenes. Many of these catalysts allow carrying out the reaction in good yields and with acceptable levels of diastereo- and enantiocontrol and some of them have also been tested with a



Scheme 8 Mechanistic scenario proposed for **26a**-catalyzed Michael reaction of aldehydes with nitroalkenes.

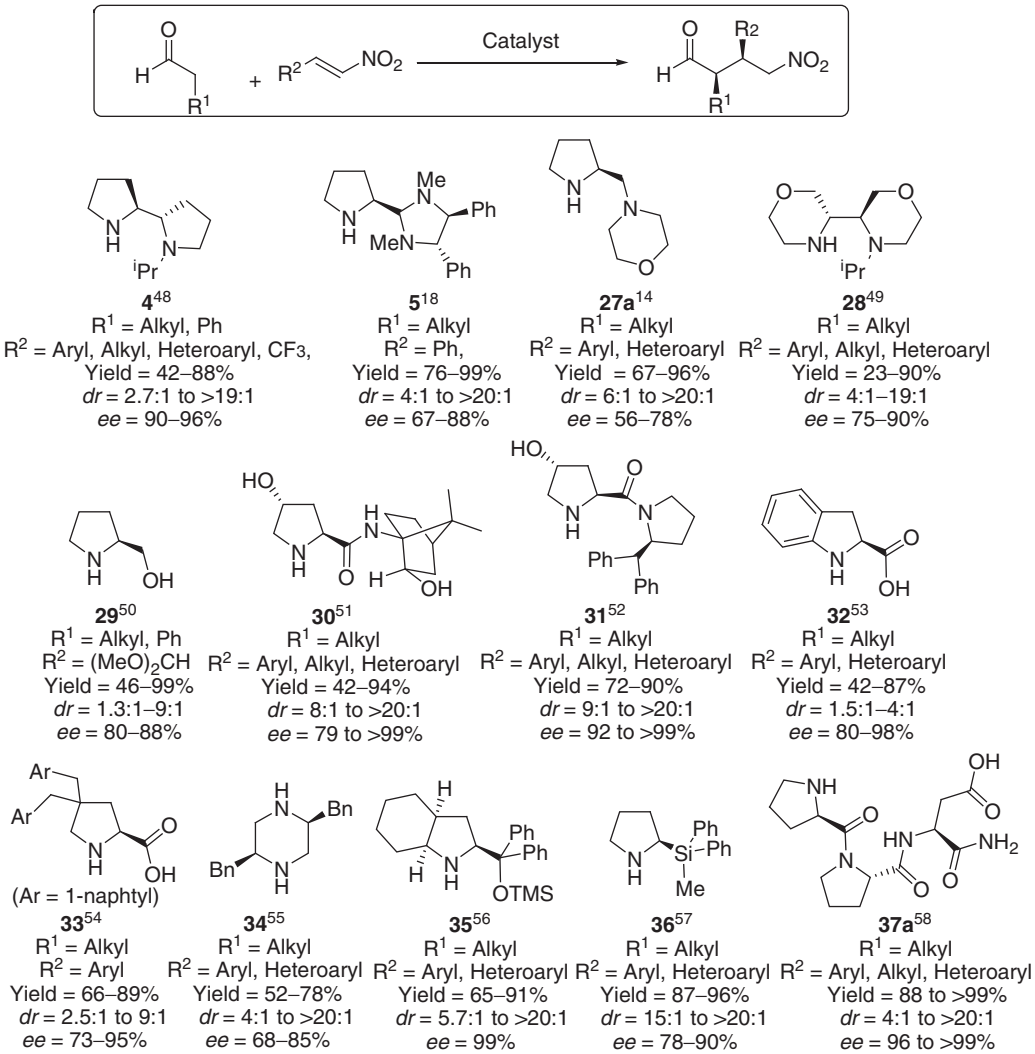
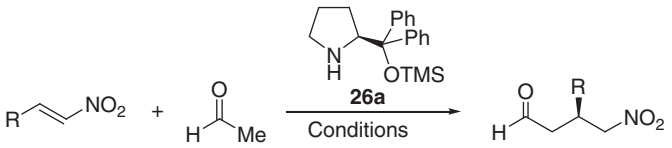


Figure 3 Catalysts employed in the Michael reaction of aldehydes with nitroalkenes under enamine activation.

wide number of very structurally different aldehyde donors and nitroalkene acceptors. However, a global analysis of all these results indicates that, in general, the results are very variable depending on the different substituents of the Michael donor and the acceptor. It has also to be mentioned that the typical reaction conditions involve the use of a rather large catalyst loading (10–20 mol%), although remarkably active catalysts such as 4-hydroxyproline-derived compound **31** and tripeptide **37a,** which can catalyze the reaction using 1–10 mol% catalyst loadings and also provide excellent yields and levels of stereocontrol.

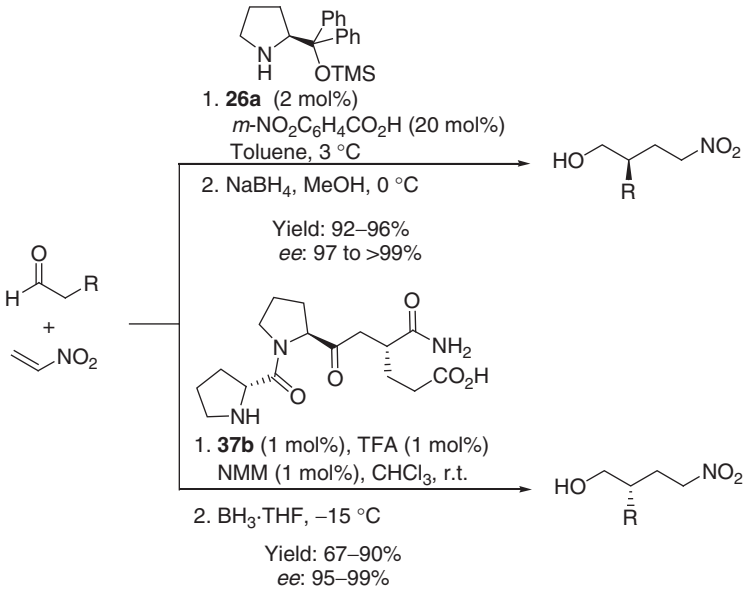
A particularly interesting situation shows up when acetaldehyde or nitroethylene are employed as Michael donors or acceptors in this reaction, which leads to the generation of a single stereocenter at the final product (Scheme 9).[59] The lack of substitution entails a much higher degree of conformational freedom in the stereodetermining step. The catalytic enantioselective conjugate addition of acetaldehyde to nitroalkenes under enamine activation has been described independently by two different research groups, both using *O*-TMS diphenylprolinol **26a** as catalyst.[60] In both cases, the initial main problem faced was to avoid the tendency of acetaldehyde to engage in self-aldol reactions via enamine intermediates, which was achieved in one case through careful manipulation of the reagent (adding a solution of freshly distilled acetaldehyde to the reaction mixture via a syringe pump) whereas in the other report the simple use of a 10-fold excess of acetaldehyde and 1,4-dioxane as the reaction solvent was reported to be enough to reach to the final Michael adducts in acceptable yields.



	Conditions	Yield	*ee*
R = Aryl or Heteroaryl	20 mol% **26a**, MeCN, 0 °C	44–58%	88–92%
R = Alkyl	20 mol% **26a**, DMF/*i*PrOH, r.t.	38–61%	88–94%
R = Alkyl, Aryl or Heteroaryl	10 mol% **26a**, 1,4-dioxane, r.t.	54–77%	92 to >99%

Scheme 9 Enantioselective Michael reaction of acetaldehyde with nitroalkenes.

With respect to the use of nitroethylene as the Michael acceptor in the Michael reaction with enolizable aldehydes, this particular reaction has been reported to proceed with excellent results, again using **26a** as the catalyst in the presence of *m*-nitrobenzoic acid[61] or, alternatively, by means of tripeptide **37b** in combination with TFA,[62] the latter system showing up as a highly active promoter for this transformation and even allowing the use of up to 1 mol% catalyst loading under optimized reaction conditions (Scheme 10). In both the cases, the Brønsted acid cocatalyst incorporated into the reaction scheme was proposed to facilitate the formation of the enamine intermediate, even though the latest findings also indicate that the additive



Scheme 10 Enantioselective Michael reaction of aldehydes with nitroethenes.

can also participate in the irreversible protonation of the enamine intermediate formed before the final hydrolysis that releases the product and the free catalyst takes place.

However, the use of α,α-disubstituted aldehydes as Michael donors entails a challenging situation but very useful and interesting from a synthetic point of view. The use of this type of aldehydes leads to the generation of a quaternary carbon atom after reaction with the nitroalkene, which typically turns into a slower reaction because of the higher steric congestion around the reaction point and also because of the difficulties associated with the formation of the enamine intermediate, which is also sterically congested. In this context, most of the amines presented in **Figure 3** have also been tested in the reaction using valeraldehyde as the Michael donor which, with a few exceptions, usually leads to a slow and less selective reaction. Alternatively, if a quaternary stereocenter is to be formed, controlling the simple diastereoselection shows up as a difficult issue, which depends on the ability of the secondary amine catalyst to induce the formation of the enamine intermediate in a well-defined configuration. For example, a secondary amine derived from proline has been tested in the reaction using α,α-disubstituted aldehydes with different substituents, although mixtures of diastereoisomers were obtained in ranges varying from 3:1 to 4.5:1 and also furnishing moderate levels of enantioselection.[63] In this sense, a straightforward solution to overcome the difficulties associated with the activation of these sterically congested aldehydes through enamine formation consists of the use of a primary amine as the catalyst, because in this case the condensation reaction is sterically more feasible and achieving the required high level of geometry control on this intermediate is also easier. Important representative examples are shown in **Figure 4,** which also show that the catalyst employed for this transformation are also bifunctional entities in which a second functionality is introduced in the catalyst structure in order to engage in H-bonding interactions with the nitroalkene acceptor. These include bifunctional sulfamide **38**,[64] L-threonine *tert*-butyl ether **39**,[65] and primary amine-thiourea **25b**,[66] the latter performing exceptionally well in the Michael reaction of α,α-disubstituted aldehydes with β-aryl substituted nitroolefins and is also particularly effective when using the more difficult and challenging β-alkyl-substituted nitroalkenes as acceptors.

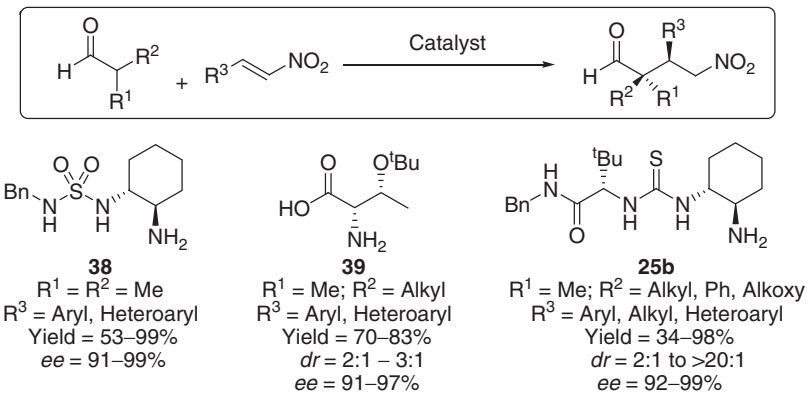
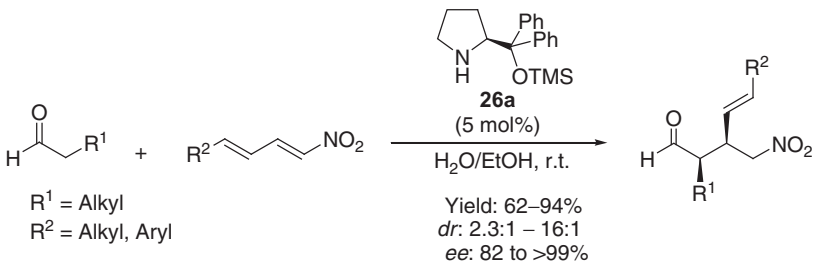


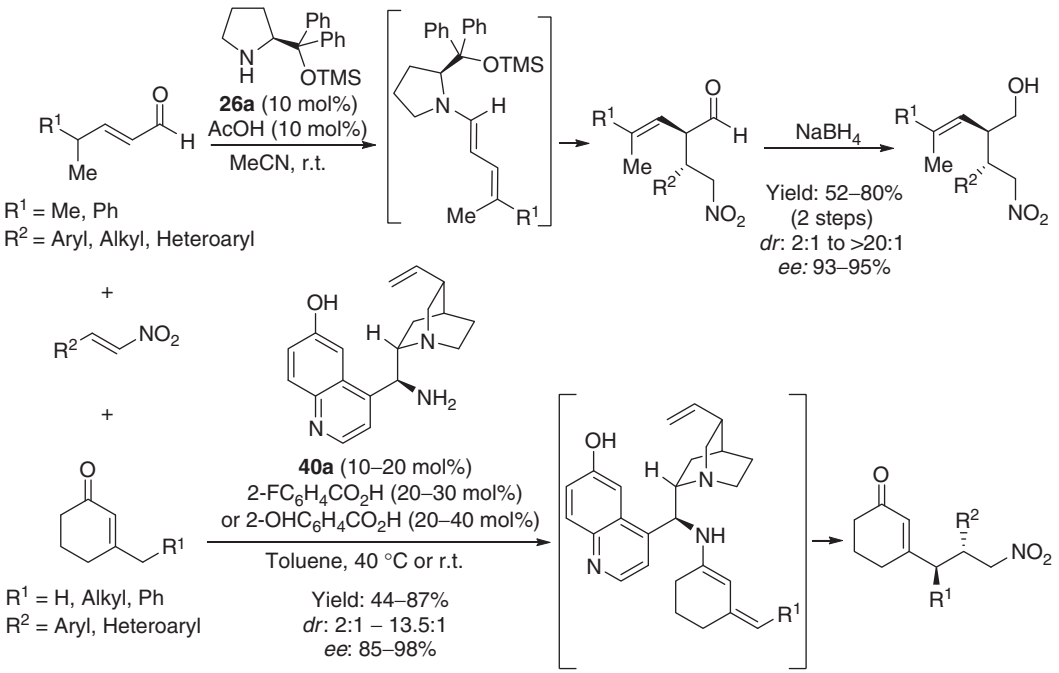
Figure 4 Several bifunctional primary amine/thiourea catalysts used in the enantioselective Michael addition of α,α-disubstituted aldehydes to nitroalkenes.

Another remarkable case is found in the use of nitrodienes as functionalized nitroalkenes (**Scheme 11**).[67] In this case, the Michael addition of aldehydes to this type α,β,γ,δ-unsaturated system proceeded with exclusive 1,4-regioselectivity when *O*-TMS-diphenylprolinol **26a** was incorporated as the catalyst. The final Michael adducts incorporating an alkene side chain were obtained in good yields and excellent enantioselectivities, although the diastereoselectivity varied depending on the substitution pattern at the aldehyde donor. Importantly, β-alkynyl nitroalkenes could also be successfully employed under similar conditions; and it has also been observed in this case that a single regioisomer had been formed as a result of a clean 1,4-addition reaction and also obtaining excellent results with regard to chemical yield and diastereo- and enantioselectivity.



Scheme 11 Enantioselective Michael addition of aldehydes to nitrodienes.

In a similar context, enolizable α,β-unsaturated aldehydes can also be used as Michael donors in this reaction although, in this case, the activation of this reagent takes place through the formation of a dienamine intermediate after condensation with the catalyst in the first step of the catalytic cycle.[68] Therefore, when these enolizable enals reacted with a variety of nitroalkenes in the presence of catalyst **26a**, a clean reaction occurred leading to the formation of an addition product containing an α-substituted β,γ-unsaturated aldehyde moiety which arose from the regioselective α-addition of this type of dienamine intermediate to the Michael acceptor (**Scheme 12**).[69] The reaction was only successful when γ,γ-disubstituted α,β-unsaturated aldehydes were employed, which were presumably needed to facilitate the formation of a more stable dienamine intermediate, and also required the incorporation of AcOH as the Brønsted acid cocatalyst. *In situ* reduction of the Michael adducts was also required, which possibly contributed to stabilize the final products and avoided the expected C=C double bond isomerization that would provide the corresponding more stable conjugated product. Dienamines generated from 3-substituted cyclohexenones behave differently, undergoing selective γ-addition in the reaction with nitroalkenes. For this reaction, cinchona alkaloid-based primary amine alkaloid **40a** was identified as the best catalyst, which proceeded smoothly furnishing the conjugate addition products in good yields and in high diastereo- and enantioselectivities.



Scheme 12 Enantioselective Michael reaction of enals and enones with nitroalkenes under dienamine catalysis.

Another issue that has led to big efforts in the field is the possibility of making use of the water compatibility of the intermediates participating in the catalytic cycle associated with enamine catalysis for carrying out the reaction in aqueous media.[70] In fact, *O*-TMS-diphenylprolinol **26a** has been found to perform well in the Michael reaction of aliphatic aldehydes with different nitroalkenes in water[71] and several other modified pyrrolidines have also been designed and employed in this reaction with different degrees of success. In this sense, the main tendency in the catalyst design has focused on the introduction of long hydrophobic alkyl side chains in the catalyst structure. The concept behind this design is the fact that the aggregation of the organocatalyst with the hydrophobic reagents participating in the Michael reaction reduces the contact between these reagents and bulk water as the reaction proceeds, thereby behaving as they were dissolved in an organic solvent. Applying this concept, it has been shown that brine and even seawater can be suitable media for carrying out the organocatalytic Michael reaction of ketones and aldehydes to nitroalkenes, using *N,N*-bis(*n*-decyl)-substituted diamine catalyst **27c** (**Figure 5**).[72] Alternatively, the use of catalysts with improved solubility in water by introducing perfluorinated alkyl side chains like in **7b**[73] or lateral amine or ammonium functionalities like in **26b**[74] at the pyrrolidine structure has also been explored and also a surfactant-type organocatalyst such as **42**[75] has been found to efficiently catalyze the Michael addition of cyclohexanone to different nitroalkenes in water with excellent results.

Other authors have focused on the development of recyclable chiral amine catalysts and, in this sense, a first approach has been focused on the use of chiral secondary amines attached to solid supports,[76] to magnetic nanoparticles,[77] or incorporated into dendrimeric structures.[78] In addition, modified chiral ionic liquid-type organocatalysts have also been used in this reaction as an alternative methodological approach toward catalyst recyclability.[79]

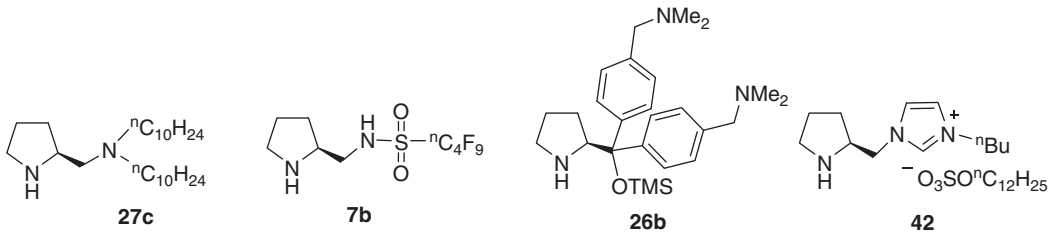


Figure 5 Some active catalysts in the Michael addition of aldehydes or ketones to nitroolefins in aqueous media.

4.03.2.1.2 α,β-Unsaturated ketones and aldehydes as Michael acceptors

The lower electrophilicity of α,β-unsaturated ketones compared with nitroalkenes typically turns into a much slower reaction and also to low conversion when trying to carry out the Michael reaction using aldehydes as Michael donors operating through enamine activation. In addition, when enones are employed as electrophiles, the chiral amine catalyst can also participate in the activation of the Michael acceptor via iminium ion formation, which also leads to some level of uncertainty when explaining the results from a mechanistic point of view, even though the formation of a chiral enamine intermediate by itself could be enough for explaining the observed stereoselectivities and might also be enough for the reaction to proceed without further activation of the Michael acceptor counterpart.[80] In this context, the Michael reaction between aldehydes and alkyl vinyl ketones has been carried out with good results using several chiral secondary amines as catalysts such as those shown in Figure 6. It is to be noted that, in all cases, the incorporation of alcohols such as hexafluoro iso-propanol, ethanol, or 4-ethoxycarbonylcatechol as additives was required for achieving high conversions, which has been interpreted in all cases in terms of their participation in the activation of the enone acceptor by hydrogen bond donation, which also supports the absence of iminium-type activation of the enone. In this sense, the reaction using imidazolidinone **43a** as the catalyst has been determined to proceed exclusively through enamine activation mechanism;[81] for the use of catalyst **44a**, the authors reported a slight nonlinear effect, which pointed toward the fact that two molecules of the catalysts could be involved in the reaction mechanism and therefore some degree of iminium-type activation of the electrophile might occur. However, the Michael reaction of ketones with enones entails a particularly difficult situation because the lower reactivity of enones as Michael acceptors is combined with the difficulties associated with the formation of the intermediate enamine of the ketone donor. In this sense, a few reports exist pertaining to these reactions that are mostly focused on the reaction of cyclohexanone or related six-membered cyclic ketones with chalcones.[82] The use of primary amines as catalysts in this transformation has only been considered in the Michael addition of cyclopentanone to chalcones[83] (Figure 6).[84–86]

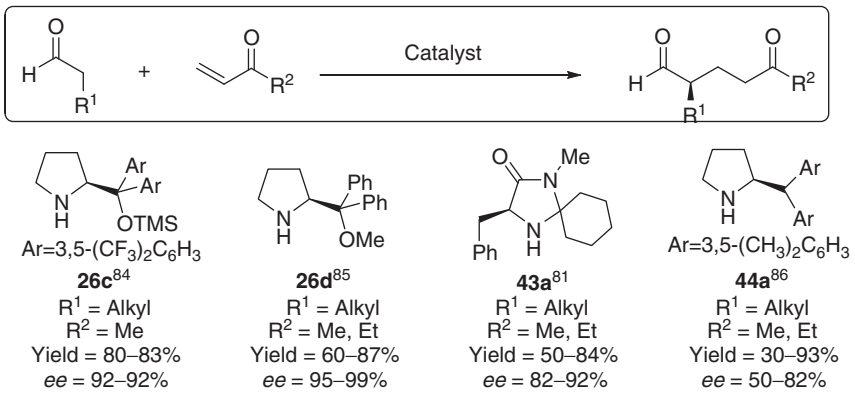
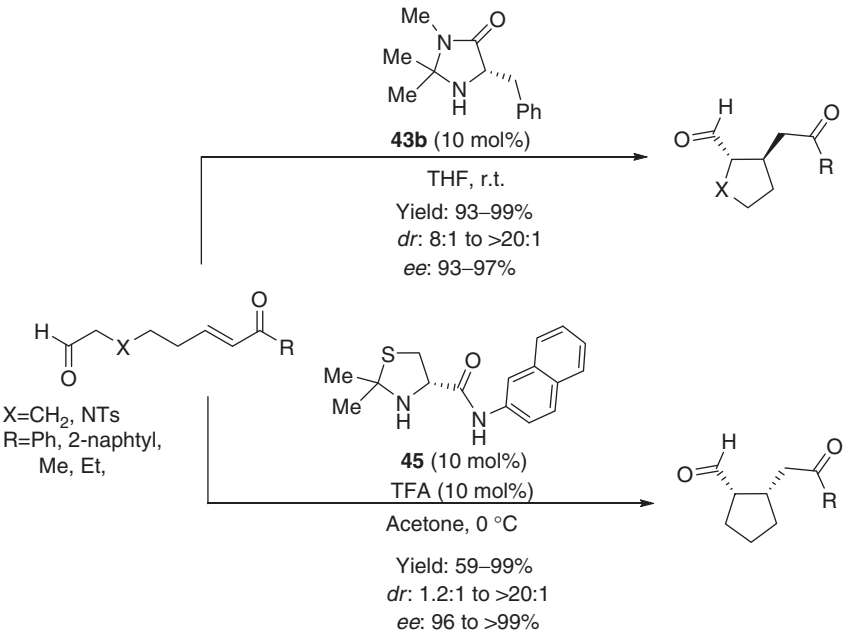


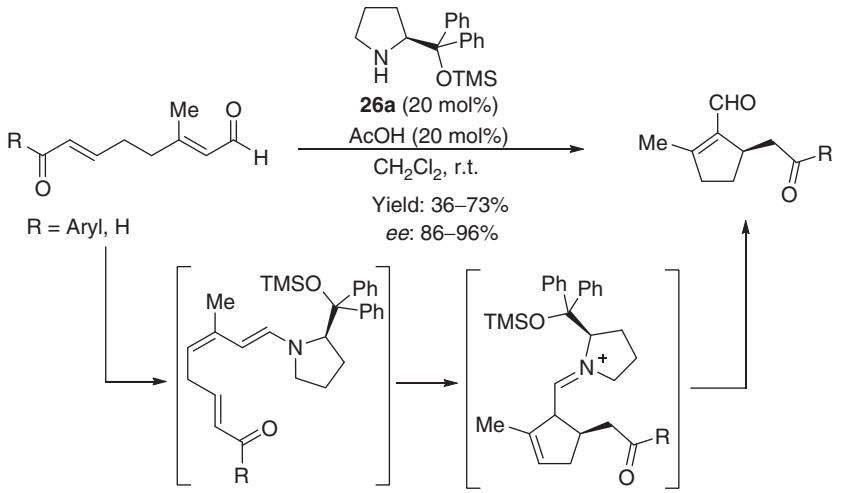
Figure 6 Chiral secondary amines employed as catalysts in the Michael reaction of aldehydes with alkyl vinyl ketones.

However, as most of these intermolecular reactions presented before have to face the already mentioned problem of limited conversion because of the lack of reactivity of the enone Michael acceptor, the related intramolecular versions usually proceed much faster. This is the case of the two examples shown in Scheme 13, in which imidazolidinone **43b** was employed as an efficient catalyst for the preparation of disubstituted cyclopentanes and pyrrolidines using a conveniently functionalized substrate containing the aldehyde donor tethered with the enone acceptor, which underwent intramolecular Michael reaction in a very efficient way.[87] Interestingly, as this **43b**-catalyzed reaction furnished *trans*-disubstituted products, an alternative approach, which made use of modified thiazolidine catalyst **45** derived from cysteine, led to the formation of the same adducts but with opposite relative configuration.[88] In this second report, a base-catalyzed isomerization process allowed the quantitative transformation of these *cis* isomers into the corresponding *trans* compounds, which indicated that the former are the kinetic products, whereas the latter *trans* diastereoisomers should be considered as the thermodynamically more stable adducts.



Scheme 13 Enantioselective intramolecular Michael reaction.

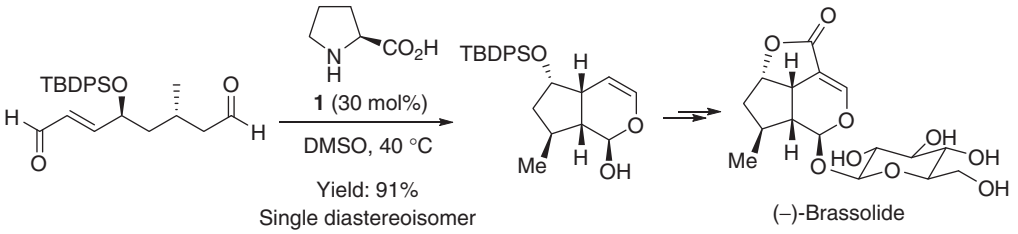
Application of the dienamine activation to this reaction scheme has also been surveyed in an elegant approach to chiral cyclopentenes, which involves the use of an α,β-unsaturated aldehyde as the Michael donor and an enone as the Michael acceptor (Scheme 14).[89] In this case, *O*-TMS diphenylprolinol **26a** was employed as a catalyst, in a reaction in which the intermediate dienamine proceeded to react with the internal electrophile through its α-carbon, leading to the formation of a cyclopentene intermediate that next underwent a C=C double-bond isomerization that generates a more stable conjugated system. The final hydrolysis for catalyst turnover accounts for the formation of the final compounds, which were isolated in moderate to good yields and in very high enantioselectivities. The reaction also performed well when another α,β-unsaturated aldehyde moiety was incorporated as the internal Michael acceptor.



Scheme 14 Enantioselective intramolecular Michael reaction using dienamine activation.

The use of α,β-unsaturated aldehydes as internal Michael acceptor has also been employed as a key step toward the total synthesis of brassolide (Scheme 15) and littoralisone,[90] the two natural products that display important biological activities. The reaction is carried out on a chiral substrate but proceeds strictly under catalyst control. In particular, the use of L-proline (**1**) as a catalyst furnished the adduct product in excellent yield and diastereoselectivity after intramolecular hemiacetal formation. The formation of this final bicyclic hemiacetal form of the reaction product was crucial for the success of the reaction because, as it happened in the previous case, this reaction was required to provide the thermodynamically less stable *cis*-diastereoisomer, which

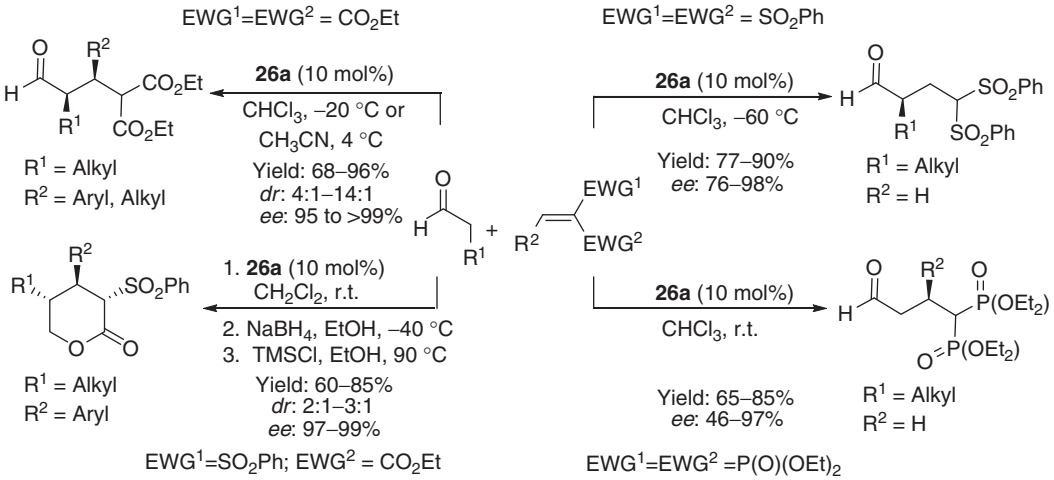
has the correct configuration required for the synthesis of the target natural product. When the reaction was carried out during prolonged reaction times, or in apolar solvents the preferential formation of the more stable open-chain *trans* diastereoisomer was formed, but when a highly polar solvent such as DMSO was used the reaction proceeded cleanly to the desired kinetic *cis* product.



Scheme 15 Enantioselective intramolecular Michael reaction for the synthesis of brassolide.

4.03.2.1.3 Other Michael acceptors

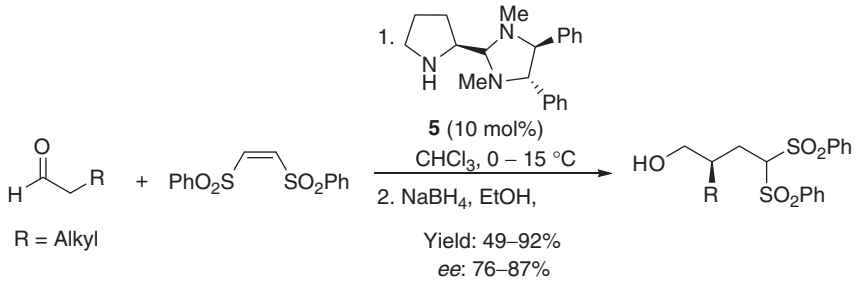
The enamine activation manifold has also been extended to other types of electron-poor olefins as Michael acceptors. However, the need for a highly reactive electrophile derived from the poor reactivity of enamine nucleophiles has limited the range of substrates amenable to be used as Michael acceptors exclusively to olefins incorporating two electron-withdrawing groups at different positions (Scheme 16). This is the case of vinyl bis(sulfones),[91] which has attracted a lot of attention mainly because of the synthetic possibilities that the sulfone group affords in terms of its wide possibilities to undergo a wide variety of transformations. Alkylidenemalonates[92] and vinyl bis(phosphonates)[93] have also been used in the same context. Doubly activated electron-poor alkenes incorporating two different electron-withdrawing groups have also been employed, which can eventually lead to the formation of three contiguous stereocenters depending on the structure of the reagents employed. However, the inherent configurational instability of the stereogenic center containing the two activating groups usually leads to the formation of mixtures of diastereoisomers. A possible solution to this problem consists in carrying out a subsequent reaction in which the formyl group present at the Michael adduct and one of these two electron-withdrawing groups participate leading to the formation of a cyclic structure in which the preferential formation of the thermodynamically more stable diastereoisomer is likely to occur. A good example is also provided in Scheme 16 in which vinylsulfones incorporating a second different activating group such as an ethoxycarbonyl moiety has led to the formation of a mixture of diastereoisomers which, on reduction/intramolecular transesterification formed the corresponding lactone with three stereocenters in which one diastereoisomer is formed in excess.[94] Other related substrates involving α-substituted vinyl phosphonates[95] or 2-acyl-substituted α,β-unsaturated esters[96] have also been employed with success. Finally, the use of ketones as Michael donors has also been faced with the help of either secondary[97] or primary[98] amine catalysts, although in general, and as expected, the latter appears to be much more efficient than the former.



Scheme 16 Michael reaction with other electron-poor alkenes under the enamine activation manifold.

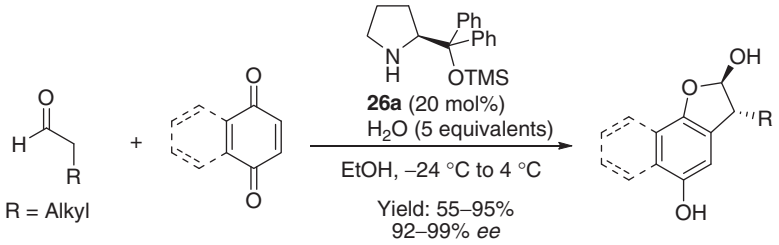
In addition to *gem*-disubstituted doubly activated olefins, alkenes incorporating two electron-withdrawing groups in α and β positions can also be employed in this transformation. This is the case of the Michael addition of aldehydes or ketones to maleimides,[99] or to γ-keto-α,β-unsaturated esters and thioesters.[100] In this context, the behavior of 1,2-bis(sulfonyl)ethane is of particular interest, because it leads to the formation of a Michael adduct with the two sulfone moieties attached to the same

carbon atom, due to the occurrence of a 1,2-sulfonyl group migration after the Michael reaction under enamine activation itself takes place (Scheme 17).[101]



Scheme 17 Michael reaction of aldehydes with 1,2-bis(sulfonyl)ethane under enamine catalysis.

Alternatively, quinones have also been used as Michael acceptors in the reaction with aldehydes under enamine activation, which results in the formal α-arylation of aldehydes after keto-enol tautomerization on the final conjugate addition product converts the quinone-based moiety into an aromatic ring (Scheme 18).[102] In this case, the final product is isolated as the corresponding hemiacetal form after intermolecular 1,2-addition of the phenol moiety to the formyl group and possibly, the formation of this stable form of the final product plays an important role as a driving force for the reaction to proceed to full conversion. Importantly, the inclusion of five equivalents of water as an additive was also found to improve conversion and stereoselectivity, which is proposed to contribute to the acceleration of the different proton transfer processes operating in the keto-enol tautomeric equilibrium, which converts the initially formed Michael adduct into the final aromatic ring.



Scheme 18 Enantioselective Michael reaction of aldehydes with quinines.

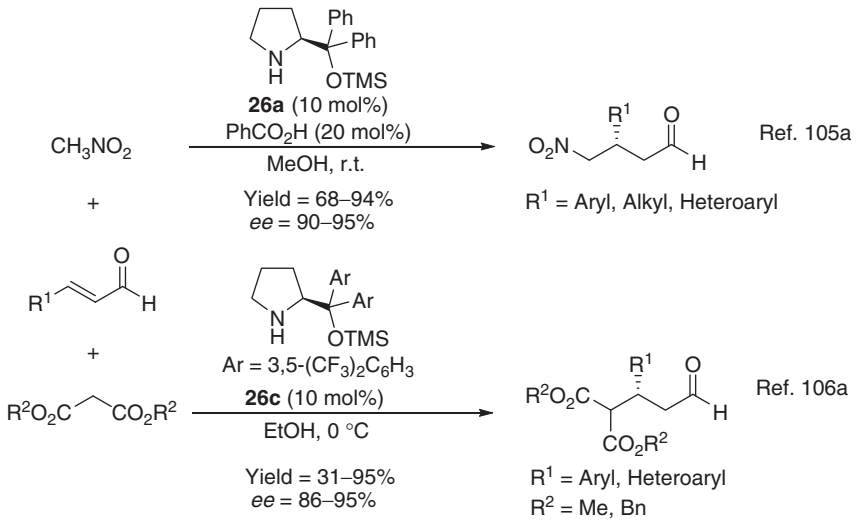
4.03.2.2 Iminium Catalysis

The iminium catalysis concept has been extensively applied to many different variants of the Michael reactions. As it was the case of the enamine catalysis, the most remarkable feature of this strategy relies on the fact that all reagents and intermediates participating in the reaction are compatible with the presence of oxygen or moisture, which turns into a very simple experimental protocol. In addition, the possibility of using α,β-unsaturated aldehydes as Michael acceptors is a relevant feature because these are not the kind of reagents that can be easily employed when working with transition metals. However, the fact that reactions under iminium activation proceed with neutral or slightly basic reaction conditions somehow limit the type of Michael donors amenable to participate in the reaction, requiring the use of a pronucleophile reagent incorporating a rather acidic C–H hydrogen that can undergo deprotonation in the reaction medium. In this context, it has been pointed out that there is a pK_a barrier for nucleophile activation in conjugate additions of carbon nucleophiles proceeding via iminium activation, which should lie between the pK_a values of 16 and 17,[103] and this is the reason why this methodology has been mostly applied to conjugate addition reactions using 1,3-dicarbonyl compounds and nitroalkanes as Michael donors. However, some other reactions have been developed in which neutral nucleophilic reagents that do not require a previous deprotonation step (like silyl enol ethers or enamides) can be directly used in this transformation under certain conditions.

4.03.2.2.1 α,β-Unsaturated aldehydes as Michael acceptors

As already mentioned, α,β-unsaturated aldehydes are very appropriate Michael acceptors to be employed in conjugate addition reactions under iminium activation by a chiral amine due to the possibility of fast and easy formation of the iminium ion intermediate through condensation with the catalyst, which is particularly effective when a secondary amine is used. In addition, this iminium ion is always preferably formed in a well-defined E geometry with respect to the C=N double bond, which turns into a very convenient situation for the chiral information present at the amine catalyst to exert stereocontrol in the

C–C bond-forming step. In this context, and after several years of intense activity in the field, *O*-trialkylsilyl-α,α-diarylprolinol derivatives **26** have been demonstrated to be a privileged family of catalysts.[104] The concept behind the catalyst design is essentially based on the presence of a very bulky diaryltrimethylsilyloxy substituent, which allows an excellent iminium geometry control and a very efficient sterical bias on the stereotopic faces of the Michael acceptor. The exceptional performance of this type of catalysts has led to their use in multiple cases of Michael reactions in which highly acidic carbon pronucleophiles such as nitroalkanes,[105] malonates,[106] cyclic 1,3-diketones[107] and β-ketoesters,[108] glycinates,[109] acetophenone,[110] β-ketosulfones,[111] β-ketosulfoxides,[112] bis-sulfonylmethanes,[113] azlactones,[114] oxindoles,[115] indolin-3-ones,[116] anthrones[117] diarylmethanes,[118] and cyclopentadiene[119] have been reacted with α,β-unsaturated aldehydes furnishing the final conjugate additions in usually good yields and in excellent enantioselectivities. Some representative examples are shown in Scheme 19. As it can be seen from this scheme, the typical reaction conditions might vary from one case to the other, depending mainly on the structure and the acidity of the carbon pronucleophile. For example, in many cases a Brønsted acid cocatalyst like benzoic acid or other related carboxylic acids are incorporated as additives in order to assist the formation of the intermediate iminium ion and in other situations, especially when the pronucleophile does not show such a high tendency to undergo deprotonation in the reaction medium, a Brønsted base cocatalyst is incorporated in order to increase the concentration of the reactive nucleophilic species.

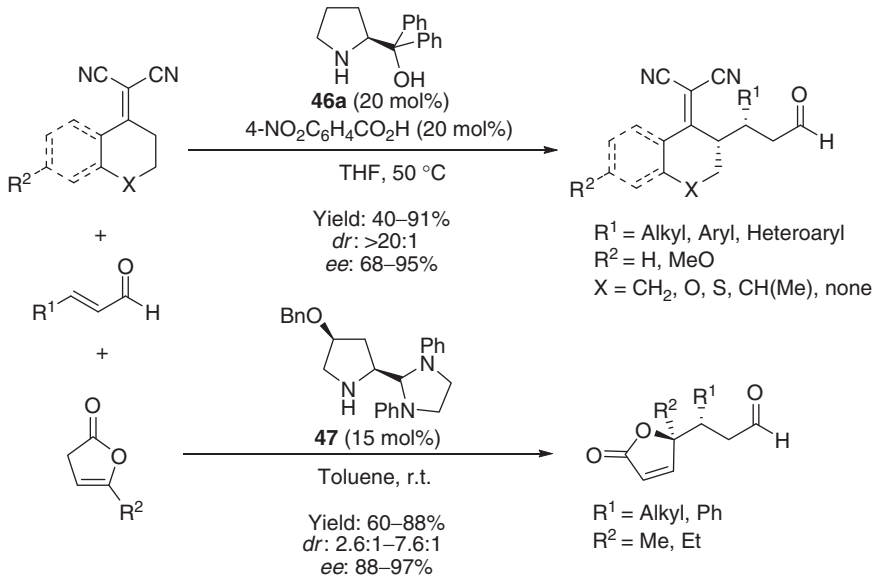


Scheme 19 Some examples of conjugate addition of C–H acidic carbon pronucleophiles to enals catalyzed by *O*-TMS-protected diarylprolinol derivatives.

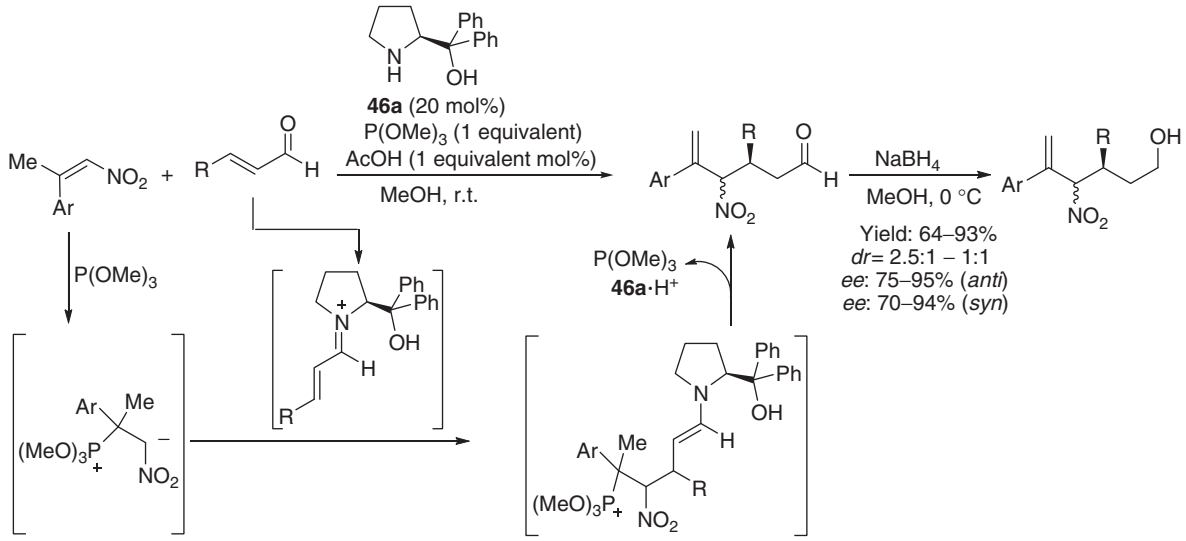
Enolizable alkylidenemalononitriles can also be used as Michael donors in this reaction by making use of the high acidity of the γ protons.[120] These type of compounds undergo γ-addition to α,β-unsaturated aldehydes in the presence of diphenylprolinol **46a** as catalyst, rendering the corresponding conjugate addition products with excellent yields and stereoselectivities and also showing a remarkable substrate scope with regard to the substitution pattern at the enal and at the benzo-fused aromatic ring present at the structure of the pronucleophile (Scheme 20).[121] Similarly, γ-butenolides have also been found to behave as suitable nucleophiles in the vinylogous conjugate addition to enals, using in this case 4-hydroxyprolinal-derived aminal **47** as an effective catalyst.[122]

A different report has shown the possibility of using nitroalkenes as Michael donors in the reaction with α,β-unsaturated aldehydes catalyzed by diphenylprolinol **46a** (Scheme 21) by incorporating one equivalent of trimethylphosphite as promoter of the reaction, the latter participating in the activation of the nitroalkene by a conjugate addition/elimination sequence similar to that operating in Baylis–Hillman reaction.[123] In this case, reaction starts with a first step in which the conjugate addition of the phosphite to the nitroalkene delivers a nitronate intermediate which next is able to undergo a conjugated addition to the iminium ion and a subsequent β-elimination, which releases the $P(OMe)_3$ reagent and a final hydrolysis step closes the catalytic cycle. Under these conditions, a wide range of different β-methyl nitrostyrenes and α,β-unsaturated aldehydes reacted with each other furnishing the corresponding Michael adducts in excellent yields and enantioselectivities, although as mixtures of diastereoisomers.

Important efforts have been carried out in order to expand the range of pronucleophiles amenable to be used under this activation mechanism which, in all the preceding cases is exclusively limited to the use of nitroalkanes or active methylene compounds. In this context, the use of carbonyl compounds containing a single activating group as Michael donors has been surveyed using trifluoroethyl thioesters as ester surrogates. The higher acidity of thioesters compared with the corresponding esters and also the incorporation of a highly electron-withdrawing fluorine-containing alkoxy substituent makes these compounds fulfill the pK_a requirement to participate as pronucleophiles in iminium-mediated Michael reactions. In fact, the catalyst **26c** was able to



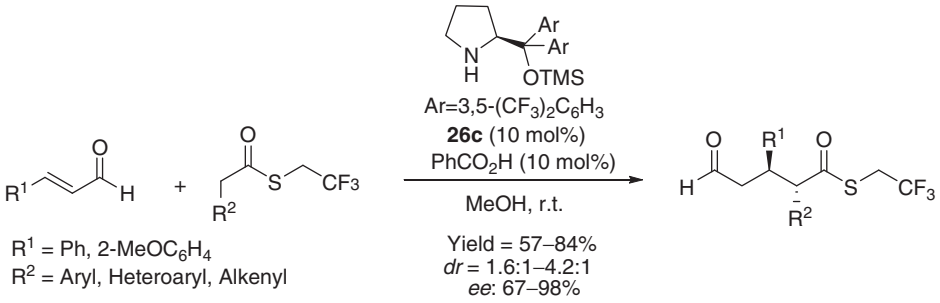
Scheme 20 Examples of vinylogous Michael reaction under iminium catalysis.



Scheme 21 Crossed Michael reaction between nitroalkenes and α,β-unsaturated aldehydes.

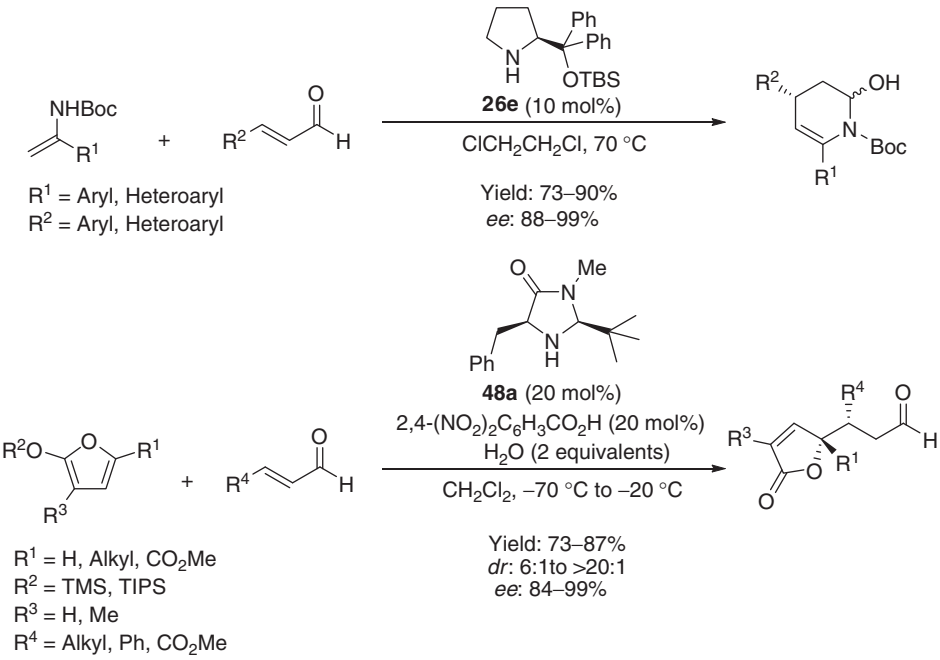
promote the Michael reaction of different arylacetic acid-derived trifluoroethyl thioesters and α,β-unsaturated aldehydes in a remarkably efficient way (Scheme 22),[103] even though the reaction was found to be limited to α-aryl-substituted thioesters, which appear over this pK_a barrier. Following a similar approach, *N*-tosylimidates, which can also be regarded as ester surrogates with comparable acidity to that of the trifluoroethyl thioesters, have also been employed in the Michael reaction with α,β-unsaturated aldehydes with similar results.[124]

An alternative approach for overcoming the requisite use of C–H acidic pronucleophiles is the previous generation of an activated form of the starting Michael donor. However, this activated pronucleophile has to be compatible with the presence of water and the amine catalyst. In this sense, enamides and silyl enol ethers can show up as useful candidates to be used as Michael donors in this process, provided that the intermediate iminium ion is reactive enough to initiate the conjugate addition process without the assistance of a Lewis acid. For example, the conjugate addition of enamides to α,β-unsaturated aldehydes can be carried out very efficiently using *O*-TBS diarylprolinol **26e** as the catalyst in a transformation that has been proposed to happen as an aza–ene reaction (concerted mechanism) although, it can also be regarded as a sequential conjugate addition of the enamine nucleophile to the iminium ion followed by hydrolysis, imine/enamine interconversion, and final hemiaminal formation. (Scheme 23).[125] However, silyl enol ethers can also be employed as nucleophiles, undergoing a typical Mukaiyama–Michael reaction with enals under iminium activation of the latter. This is the case of the imidazolidinone **48a**-catalyzed enantioselective



Scheme 22 The Michael reaction of trifluoroethyl thioesters with α,β-unsaturated aldehydes under iminium activation.

conjugate addition of silyloxyfuranes to α,β-unsaturated aldehydes, providing a direct and efficient route to the γ-butenolide architecture (Scheme 23).[126] This reaction was needed for the incorporation of 2,4-dinitrobenzoic acid (DNBA) as a Brønsted acid cocatalyst assisting the formation of the intermediate iminium ion, and also two equivalents of water had to be included as additive for the reaction to proceed to completion, and which were required in order to overcome the loss of water from the catalytic cycle because of the generation of the trimethylsilyl cation, which eventually does not allow catalyst turnover. Under the optimized conditions, the reaction proceeded with good yields and with excellent levels of stereocontrol for a series of α,β-unsaturated aldehydes and different silyloxyfuranes. Moreover, the performance of this reaction has been demonstrated with some very elegant examples of its application to total syntheses of natural products.[126a,127]

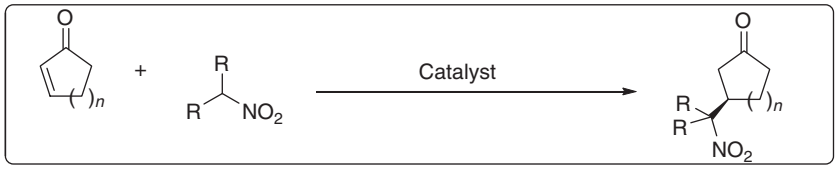


Scheme 23 Examples showing the use of enamides and silyl enol ethers as Michael donors in enantioselective Michael reactions to α,β-unsaturated aldehydes.

4.03.2.2.2 α,β-Unsaturated ketones as Michael acceptors

The lower reactivity of ketones toward condensation with amines entails a challenging situation when trying to carry out a Michael reaction using enones as acceptors using the iminium activation approach. Despite this, it should be mentioned that one of the first examples of a Michael reaction under iminium catalysis reported in the chemical literature refers to the use of rubidium prolinate for promoting the Michael reaction between malonates or nitroalkanes with cyclohexenone, although enantioselectivities remained moderate in almost all the cases.[128] More recently, and once the iminium activation concept had been fully recognized and identified as a general organocatalytic tool for the activation of Michael acceptors, other alternative and highly efficient methodologies have been developed for this particular reaction. However, with respect to the Michael donor reagent, it should be mentioned that this approach has been restricted to the use of acidic carbon pronucleophiles like nitroalkanes, malonates, and other 1,3-dicarbonyl compounds.

Regarding the use of nitroalkanes as Michael donors, the simple proline **1** had been rather early identified as a suitable catalyst in the conjugate addition of nitroalkanes to cycloalkenones,[129] and afterwards several other proline-based catalysts like **2**,[130] **49**,[131] **50**,[132] or **51**[133] have been studied, with different degrees of success and mostly using cyclic enones as Michael acceptors (Figure 7). Remarkably, in all these examples, a basic additive had to be incorporated in the reaction either as a cocatalyst or as a



1[129]
R = Me, –$(CH_2)_4$–, –$(CH_2)_5$–
n = 1,2,3
Yield = 49–88%
ee = 75–93%

2[130]
R = H, Me, –$(CH_2)_5$–
n = 1, 2
Yield = 49–70%
ee = 75–98%

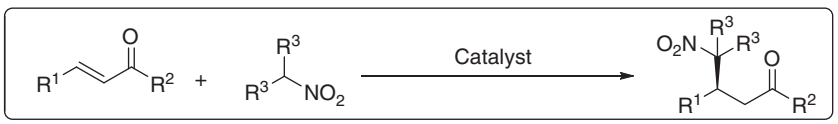
49[131]
R = Me, –$(CH_2)_4$–, –$(CH_2)_5$–
n = 1,2,3
Yield = 50–93%
ee = 61–91%

50[132]
R = H, Me
n = 1,2
Yield = 18–78%
ee = 72–80%

51[133]
R = H, Me, –$(CH_2)_4$–, –$(CH_2)_5$–
n = 1, 2
Yield = 24–95%
ee = 58–84%

52a[134]
R = H, Me
n = 1, 2
Yield = 70–92%
ee = 80–98%

53a[135]
R = H, Me
n = 1,2,3
Yield = 73–90%
ee = 88–99%



2[130]
R^1= Aryl, Alkyl, CO_2Et
– R^2= Me, Et
R^3 = H, Me, –$(CH_2)_5$–
Yield = 44–80%
ee = 58–89%

54a[136]
R^1 = Aryl, heteroaryl
R^2 = Me, Et
R^3 = H, Me, –$(CH_2)_4$–, –$(CH_2)_5$–
Yield = 82–97%
ee = 64–92%

52a[134]
R^1 = Aryl, Alkyl, heteroaryl
R^2= Me
R^3 = H, Me
Yield = 80–96%
ee = 73–85%

55[137]
R^1= Aryl, Alkyl, heteroaryl
R^2 = Alkyl
R^3 = H, Me
Yield = 38–89%
ee = 92–99%

56a[138]
R^1 = Aryl, Alkyl, heteroaryl
R^2 = Me, Et, Ph
R^3 = Me
Yield = 62–99%
ee = 87–92%

Figure 7 Organocatalysts employed in the Michael reaction of nitroalkanes with enones.

stoichiometric additive which is supposed to participate in the generation of the reactive nitronate nucleophile. The better ability of primary amines to engage in condensation reactions with enones has also been employed in this context and, for example, bifunctional primary amine-thiourea catalyst **52a** has been surveyed in this reaction furnishing, in general, higher yields and enantioselectivities than the other secondary amine catalysts and also showing a remarkable substrate scope regarding the Michael donor, allowing the use of both cyclic and acyclic enones.[134] Moreover, the bifunctional nature of the catalyst also allowed carrying out the reaction without the need of any external base additive. Additionally, primary amine **53a** was also able to promote the reaction of nitromethane with 3-alkyl substituted cyclohexenones, thereby generating a quaternary stereocenter after the conjugate addition process.[135] It should also be underlined that when nitroalkanes with different substituents at the α-carbon were employed, the final products were typically obtained as mixtures of diastereoisomers in ratios ranging from 1:1 to 1:5, which is still an unsolved issue associated with this reaction, in a clear parallelism to the behavior of the same reaction in which α,β-unsaturated aldehydes were used as Michael acceptors. However, the use of acyclic enones with enhanced degree of conformational freedom has typically ended up in poorer results with most of these catalysts shown before, especially in terms of enantioselectivity. As a consequence, novel catalyst structures have been conveniently designed and developed for being used in this particular transformation (see **Figure 7**). For example, imidazolidine **54a** has been successfully employed in this reaction, showing a good behavior, once again in the reaction with different β-aryl-substituted enones.[136] However, proline tetrazole analog **2** afforded similar results as those furnished by **54a**, that is, good-to-moderate yields and excellent enantioselectivities up to 91% *ee*,[130] whereas bifunctional primary amine catalysts **52a**,[134] **55**,[137] and **56a**[138] showed an excellent performance in the reaction, being active in the Michael reaction of nitroalkanes to alkenyl methyl ketones and providing very high enantioselectivities. Also in all these cases, the use of unsymmetrically substituted nitroalkanes led to mixtures of diastereoisomers in variable ratios.

Malonates are another class of acidic pronucleophiles, which have been used in the conjugate addition reaction to enones under iminium activation and, in this sense, most of the catalysts shown in **Figure 7**, have also been tested in this reaction, showing a behavior similar to that observed in the parent reaction in which nitromethane was employed as the pronucleophile. A selection of catalysts used to promote this transformation is shown in **Figure 8**, which includes several chiral secondary amines such as imidazolidine **54b**,[139] proline-tetrazole **2**,[140] and other related proline-based secondary amines like **57**[141] and **58**[142] together with a set of different chiral primary amines like **52b**[143] and **56b**.[144] In addition, other related highly acidic 1,3-dicarbonyl compounds can also be employed with success under this reaction scheme. This is the case of β-ketoesters, for which primary-thiourea **52b** was used as the catalyst[145] and the case of nitroacetates, in which primary amine **53a** has shown to perform very efficiently in the Michael reaction with a wide range of β-aryl- and β-alkyl-substituted enones.[146] The closely related quinine-based primary amine **40b** has been identified as a useful catalyst for the Michael reaction of bis(sulfonyl)methane and acrylonitrile to acyclic enones[147] and, in a different report, the conjugate addition of oxindoles to chalcones catalyzed by **53b** has also been shown to proceed with excellent yields and stereoselectivities.[148]

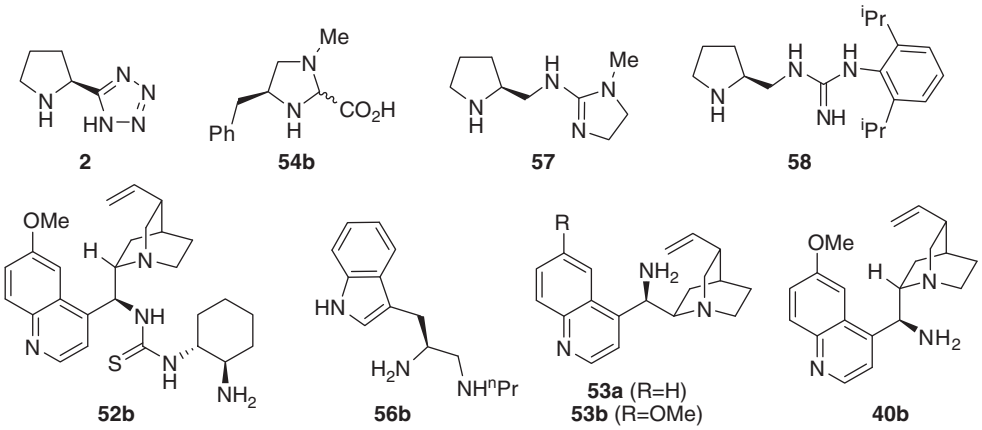
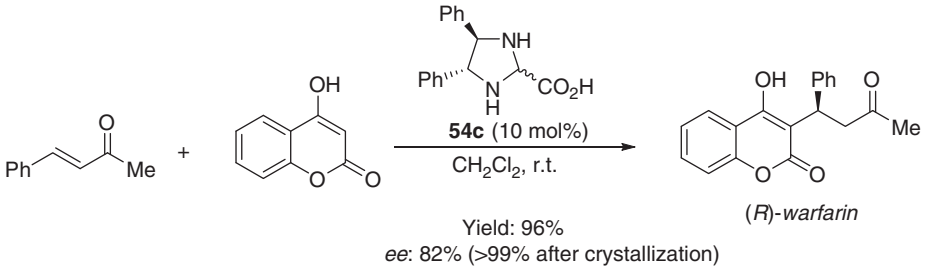


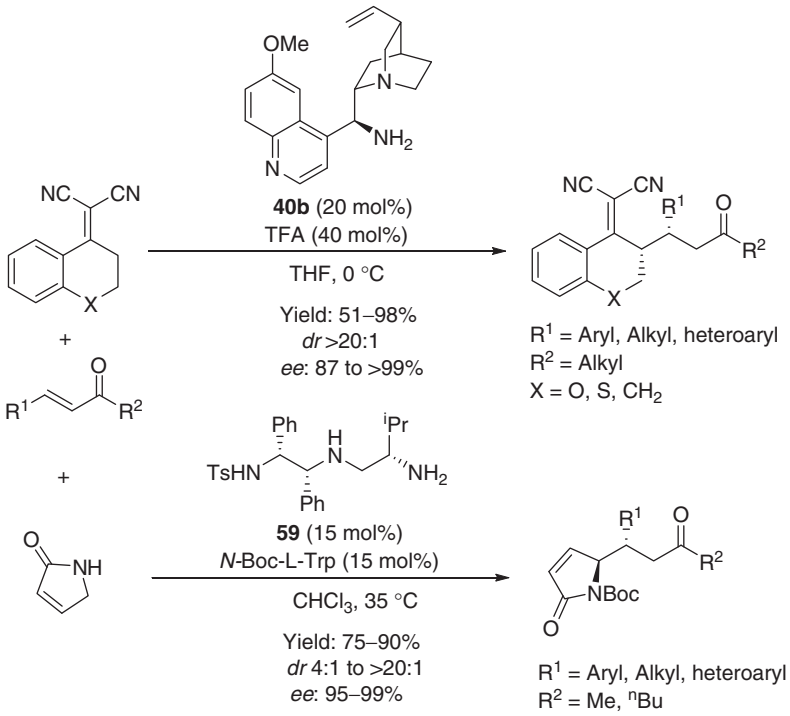
Figure 8 Organocatalysts employed in the Michael reaction of malonates and related compounds with enones.

In addition, many different research groups have focused on the use of cyclic 1,3-dicarbonyl compounds as Michael donors, mainly because warfarin, an anticoagulant generic drug, can be directly prepared using this reaction (see **Scheme 24**). In this context, modified imidazolidine catalyst **54c** has shown its outstanding performance in the Michael reaction of a wide range of different cyclic 1,3-dicarbonyl compounds with acyclic enones, showing a remarkably wide substrate scope regarding the substitution pattern at the Michael acceptor.[149] Even though enantioselectivities remained at approximately 80% *ee* in most cases, usually more than 99% *ee* could be obtained after a single recrystallization process. The example presented in **Scheme 24** represents the direct synthesis of (*R*)-warfarin and this reaction could be scaled up to 1 kg scale without any decrease in yield or enantioselectivity. Other different catalytic systems have been developed later for the preparation of warfarin with variable results.[150]



Scheme 24 Enantioselective synthesis of (*R*)-warfarin.

Finally, several cases of a vinylogous Michael addition have been described in which enolizable α,β-unsaturated compounds with a highly acidic γ-proton undergo smooth conjugate addition with enones under the iminium activation scheme (Scheme 25). This is the case of α,α-dicyanoolefins for which the chiral primary amine **40b** was found to catalyze the reaction with a variety of enones furnishing the desired Michael adducts in good yields and excellent enantioselectivities.[151] *N*-Boc-1,5-dihydro-pyrrol-2-one behaved similarly via participation of vinylogous enolate nucleophilic species, giving rise to the formation of the corresponding conjugate addition products with high yields and an outstanding chemo- and diastereoselectivity in the presence of triamine catalyst **59**.[152] In this case, N-Boc-protected tryptophan had to be used as Brønsted acid cocatalyst and, due to the chiral nature of this additive, the corresponding matched combination of reagents had to be identified. Other reports have also employed γ-butenolides as equally effective Michael donors that are able to undergo vinylogous Michael reaction in the presence of other chiral primary amines like **59** itself or other chiral primary amines.[153]



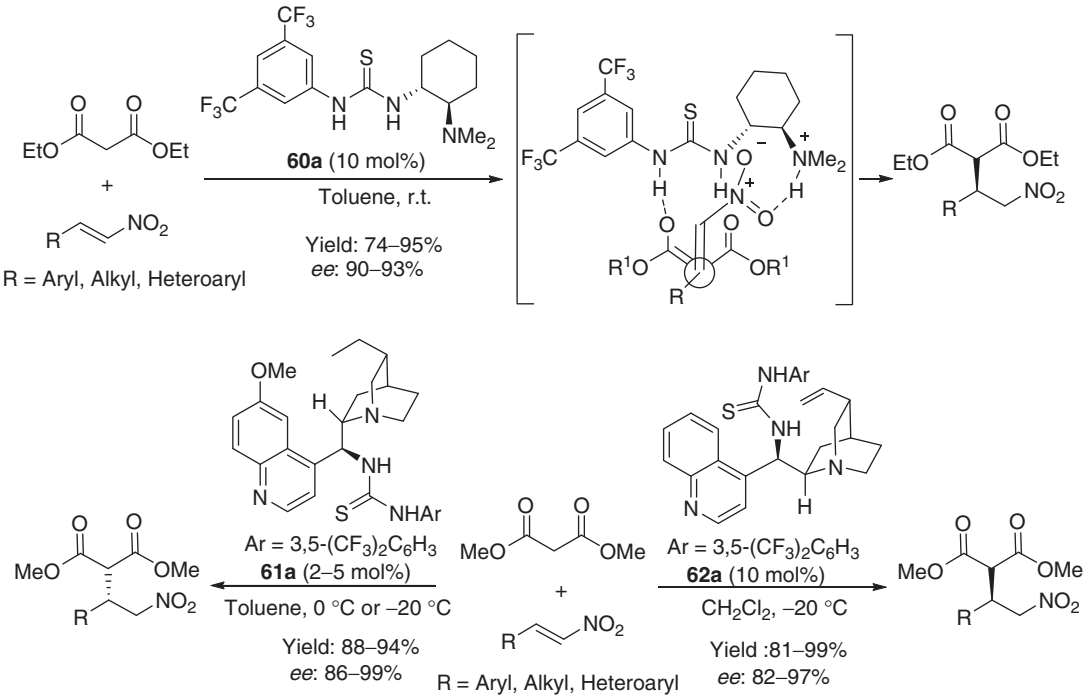
Scheme 25 Enantioselective vinylogous Michael reactions under iminium activation using enones as acceptors.

4.03.2.3 H-Bonding Catalysis

As mentioned in Section 4.03.1, an alternative option for an organic molecule to catalyze the Michael reaction consists of the activation of the acceptor through hydrogen-bonding interactions, which releases electronic density from the olefin and, at the same time, provides the required steric bias for stereocontrol. As it also happened in the iminium activation, compounds incorporating a rather acidic C–H hydrogen have to be used as pronucleophiles because the activation of the Michael donor by deprotonation with strong bases is not compatible with the acidic protons of the catalyst. It has to be pointed out that less acidic pronucleophiles such as enolizable aldehydes and ketones can also be used as Michael donors under this activation manifold, but these require their previous activation as the corresponding enamine, needing for a bifunctional catalyst containing both a primary/secondary amine and an H-donor site and these cases have been specifically covered in Section 4.03.2.1.

4.03.2.3.1 Nitroalkenes as Michael acceptors

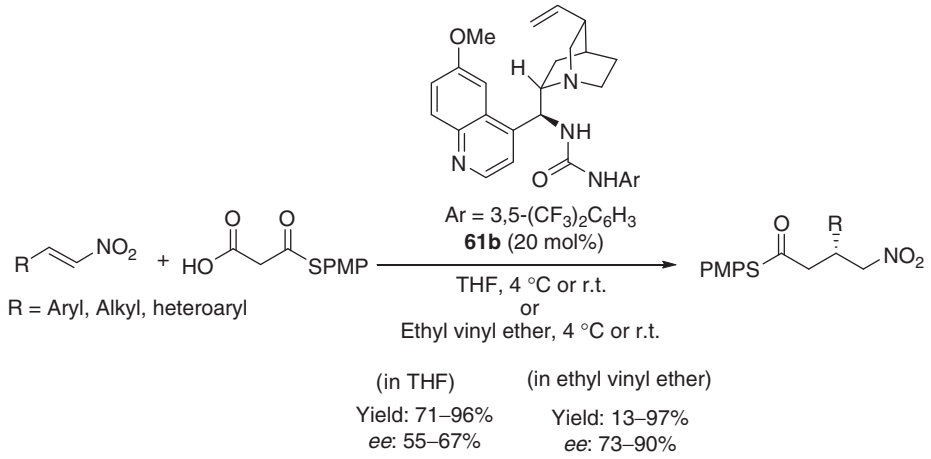
Chiral thioureas have been found to be outstanding catalysts for promoting the Michael reaction of acidic pronucleophiles to nitroalkenes, mainly because of the known ability of this functional group for engaging in selective H-bonding interactions with the nitro group due to the effective formation of two hydrogen bonds between the NH groups and the highly electron-rich oxygen atoms of the nitro moiety.[154] This thiourea–nitroalkene interaction is rather strong, occurring even in the presence of water molecules and also guarantees a highly chemoselective reaction if other basic groups or potential Michael acceptor moieties are present at the substrate structure. The first example of one of these catalysts specifically designed for the Michael reaction of malonates with nitroalkenes is the bifunctional thiourea **60a** (Scheme 26).[155] This incorporates the usual *N*-aryl-substituted thiourea moiety together with an additional dimethylamino basic site placed at a convenient position on the chiral backbone, which is proposed to contribute to catalyst activity through activation of the pronucleophile activate through deprotonation. However, subsequent experimental and theoretical studies have pointed out that the reaction most likely proceeds through the activation of the enolate nucleophile (formed after a previous first deprotonation step) through double H-bonding interaction with the thiourea moiety, whereas the nitroalkene would engage in a single H-bonding interaction with the protonated dimethylammonium moiety.[156] Chiral thioureas derived from cinchona alkaloids represent another family of highly efficient bifunctional catalysts that have been successfully employed in this transformation. The high proficiency of this type of catalysts relies on the presence of the basic quinuclidine nucleus close to the thiourea moiety in a well defined chiral environment, which results in a very successful architecture for promoting the conjugate addition of malonates to nitroalkenes and allowing the use of remarkably low catalyst loadings.[157] In this sense, 9-*epi*-cinchonine-derived thiourea **61a** was also reported to be a very efficient catalyst for this reaction,[158] obtaining the final Michael adducts in excellent yields and enantioselectivities and with the opposite configuration than the products obtained in the related **62a**-catalyzed reaction due to the pseudoenantiomeric nature of this catalyst with respect to **61a**. This methodology, using either these catalysts or other closely related ones has been employed by several authors for the enantioselective synthesis of different biologically active compounds, showing the utility of this approach as a very efficient and general tool in synthesis.[159] Moreover, these catalysts have also been shown to perform well with other 1,3-dicarbonyl compounds such as *β*-ketoesters or 1,3-diketones. Following this design, subsequent intensive research efforts have led to the development of a wide number of other chiral bifunctional tertiary amine-thiourea catalysts that have been tested with success in this reaction using a variety of different 1,3-dicarbonyl compounds or related C–H acidic carbon pronucleophiles as Michael donors.[160]



Scheme 26 Two different families of chiral tertiary amine-thiourea catalysts with an outstanding performance in the Michael reaction of malonates and related compounds with nitroalkenes.

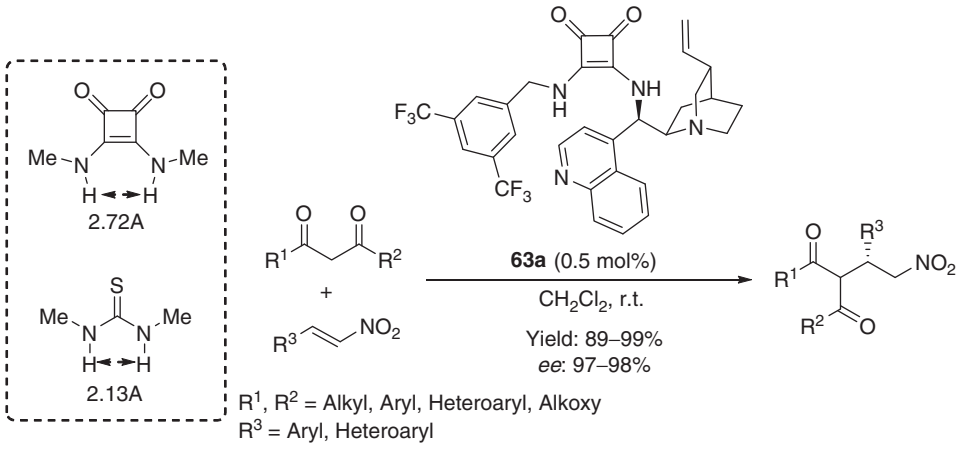
A related work has shown that malonic acid half-thioesters can be employed as acetyl carbanion equivalent in the Michael reaction with nitroalkenes using this kind of activation, leading to the direct formation of *γ*-nitrothioesters through a decarboxylation process, which takes place after or during the conjugate addition step. In this case, bifunctional cinchona-based urea **61b** was identified as the best catalyst for the reaction,[161] whereas the corresponding thiourea was found to be significantly

less active in the model reaction (Scheme 27).[162] The reaction outcome was highly dependent on the experimental conditions employed showing that the reaction proceeded in excellent yields and moderate enantioselectivities when THF was used as the solvent, whereas enantioselectivities up to 73–90% *ee* could be obtained with ethyl vinyl ether, but with a remarkable decrease in the yield of the process. A very important feature associated with this reaction is the fact that the use of *β*-alkyl-substituted nitroalkenes as Michael acceptors, which are challenging substrates that typically show a poorer performance in other cases, did not result in a particularly complicated situation, behaving in a similar way as the nitrostyrene derivatives.



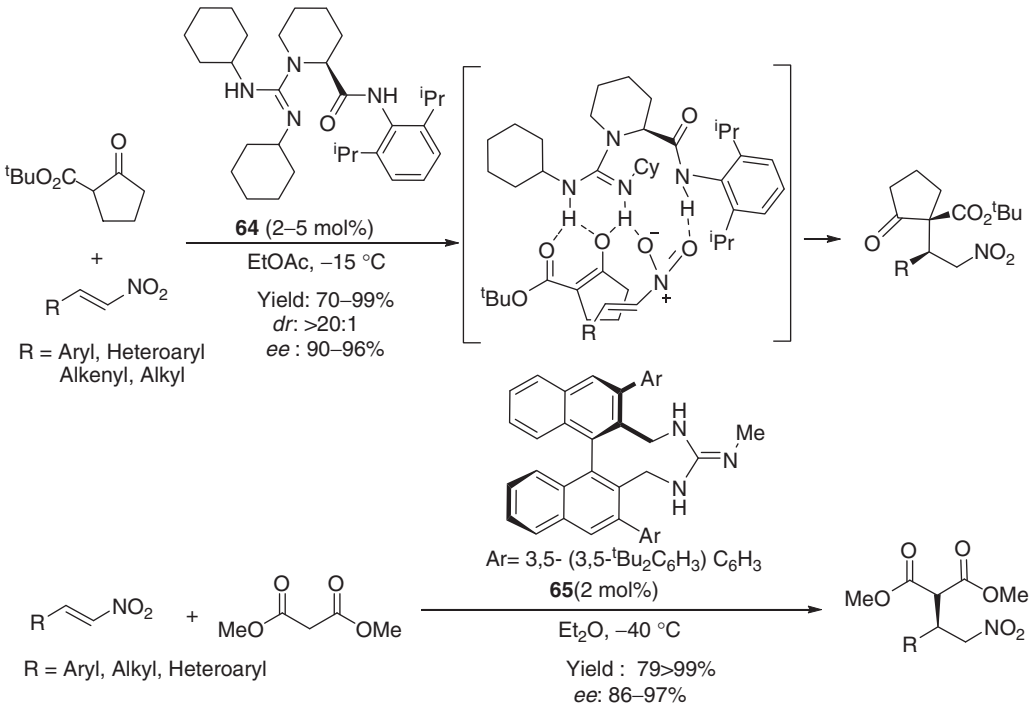
Scheme 27 Enantioselective Michael addition of malonic acid half-thioesters to nitroalkenes.

Evolution in the design of this type of bifunctional catalysts has resulted in the identification of the squaramide moiety as a different privileged platform for the activation of nitro or other related groups by the formation of a well defined H-bonding network (see Scheme 28).[163] The aromatic character of the squaramide unit leads to a planar and more structurally rigid structure, which facilitates the formation of the H-bonded network and can also lead to the formation of more conformationally rigid intermediates in the corresponding reaction in which they participate as catalysts. Furthermore, the differences in the distances between the two donating hydrogens and the C–N–H bond angles when compared with the related thiourea functionality show that the N–H group in squaramide lies in a more convergent orientation toward the H-bonding acceptor basic site, which leads to a better ability for releasing electron-density from the nitroalkene on binding. These features have been exploited by several research groups and, in fact, chiral squaramides have revealed as outstanding catalysts for different cases of enantioselective Michael reactions.[164] The first reported example,[163] which is also very illustrative of the capacities of this structure for the activation of electrophiles through H-bonding interactions, is related to the Michael reaction of 1,3-diketones with nitroalkenes using cinchona-alkaloid based catalyst **63a**, which proceeds smoothly, furnishing the corresponding adducts with excellent yields and enantioselectivities. However, the most remarkable feature of this reaction is the low catalyst loading, showing that the reaction can be completed in acceptable times (approximately 7 h) with only 0.5 mol% of **63a**, a clear indication of the high activity and performance of this type of chiral catalysts in terms of both chemical efficiency and stereocontrol.



Scheme 28 Squaramides as catalysts in the enantioselective Michael addition of 1,3-diketones to nitroalkenes.

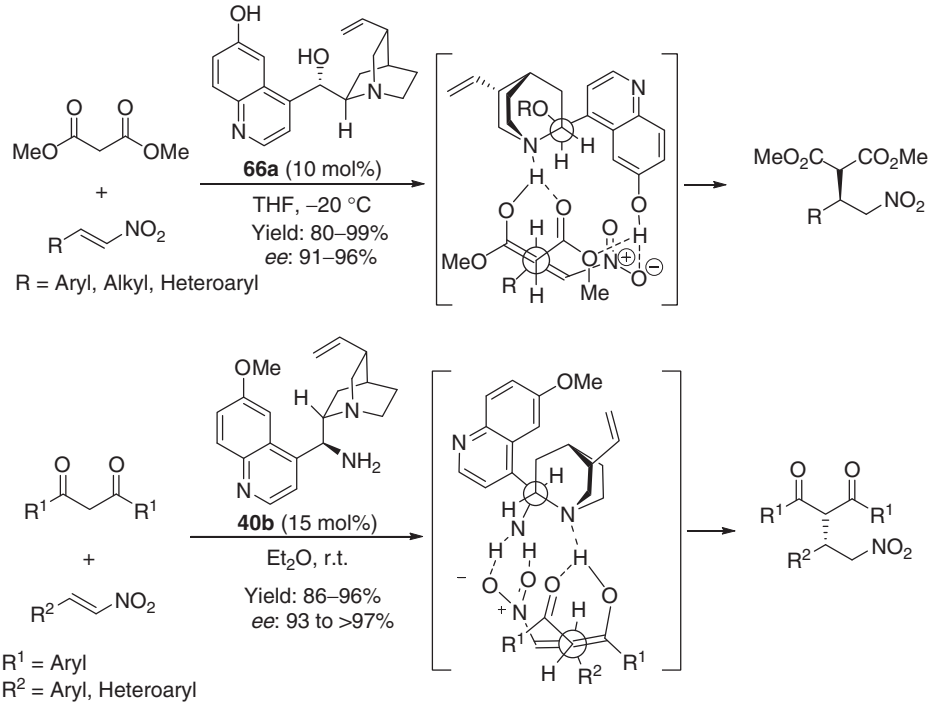
Catalysts incorporating other functionalities which are also capable of engaging in H-bonding interactions with the nitro group through hydrogen bonding have been surveyed in this reaction. For example, chiral bifunctional guanidine such as **64** constitutes a representative example, which has shown excellent performance in the Michael addition of cyclic β-ketoesters to nitrostyrene derivatives (Scheme 29).[165] This bifunctional catalyst is proposed to activate the pronucleophile by deprotonation assisted by the highly basic guanidine moiety and in addition, this guanidine group was also proposed to engage in multiple hydrogen-bonding interactions with both the nitroalkene and the enolate nucleophile, the latter also establishing an additional H-bond with the lateral secondary arylamide moiety. This multiple array of H-bonding interactions leads to a very well-ordered arrangement of the reagents in the transition state and accounts for the excellent diastereo- and enantioselectivities achieved. Moreover, **64** was also found to be a very active catalyst (catalyst loadings up to 2 mol%), which has been interpreted in terms of the strongly basic character of the guanidine moiety that enables a very effective deprotonation of the pronucleophile. Another very active guanidine-type catalyst containing an axially chiral backbone (**65**) has already been reported before in the reaction of dimethylmalonate to nitroalkenes (Scheme 29),[166] although in this case, it did not incorporate any other secondary functionality for establishing multiple interactions with both the Michael donor and the acceptor, the incoming trajectory of the electrophile being controlled by the axial chirality of the catalyst and, in particular, by the presence of the bulky 3,6-bis(3,5-di-*tert*-butylphenyl)phenyl groups placed at the 3 and 3′ positions of the binaphthyl backbone. There is also a modified version of thiourea **60a**, which incorporates a benzimidazole heterocycle as the H-bonding donor site in place of the thiourea moiety, which has been tested with success in several Michael-type reactions of 1,3-dicarbonyl compounds to nitroalkenes.[167]



Scheme 29 Enantioselective Michael reactions to nitroalkenes catalyzed by chiral guanidines.

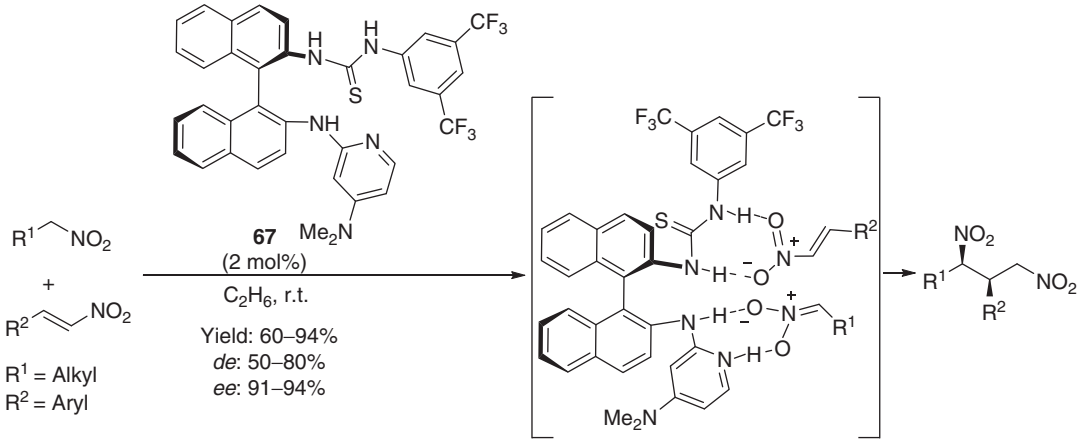
Molecules that participate in the activation of the electrophile by the donation of a single hydrogen bond have also been shown to be efficient catalysts for this reaction. In particular, simple modified cinchona alkaloids such as cupreidine (**66a**),[168] is able to promote the Michael reaction of dimethylmalonate with nitrostyrenes furnishing excellent yields and enantioselectivities (Scheme 30)[169] and further work has shown that the catalyst is able to promote the reaction using a wide range of 1,3-dicarbonyl compounds.[170] A stereochemical model has also been proposed, which accounts for the observed results (Scheme 30), indicating that the activation of the electrophile should occur via H-bonding interaction with the phenolic OH group and the quinuclidine basic moiety would be involved in the activation of the 1,3-dicarbonyl pronucleophile. Another very effective related catalyst (**40b**) has been developed in which starting from the same basic scaffold, the secondary alcohol moiety was changed to an amino group with the opposite configuration at the carbon atom and, in addition, the phenolic group was modified as the corresponding methyl ether. This catalyst has been found to promote the Michael addition of 1,3-diaryl-1,3-propanediones to nitroalkenes with excellent results.[171] Importantly, as this catalyst **40b** cannot activate the electrophile via H-bonding interaction through the phenolic OH group, the primary amine group is proposed as a new H-donor site involved in the activation of the nitroalkene. The opposite configuration of this C-9 stereogenic center in this catalyst is also crucial for stereocontrol because the corresponding epimer was found to perform very poorly in the same reaction. This indicates that in the 9-*epi*-amino cinchona alkaloid series, the catalyst can adopt a correct low energy conformation that delivers the Michael donor and the acceptor close to each other much

more easily. Finally, it has also to be pointed out that very simple and small aminoalcohols like αα-diarylprolinols have also been found to catalyze the Michael reaction of malonates with nitrostyrenes, although in moderate enantioselectivities in which it is proposed that the catalyst activates the nitroalkane by establishing a single H-bonding interaction via its OH group and the remaining secondary amine functionality would engage in the activation of the nucleophile via deprotonation.[172]



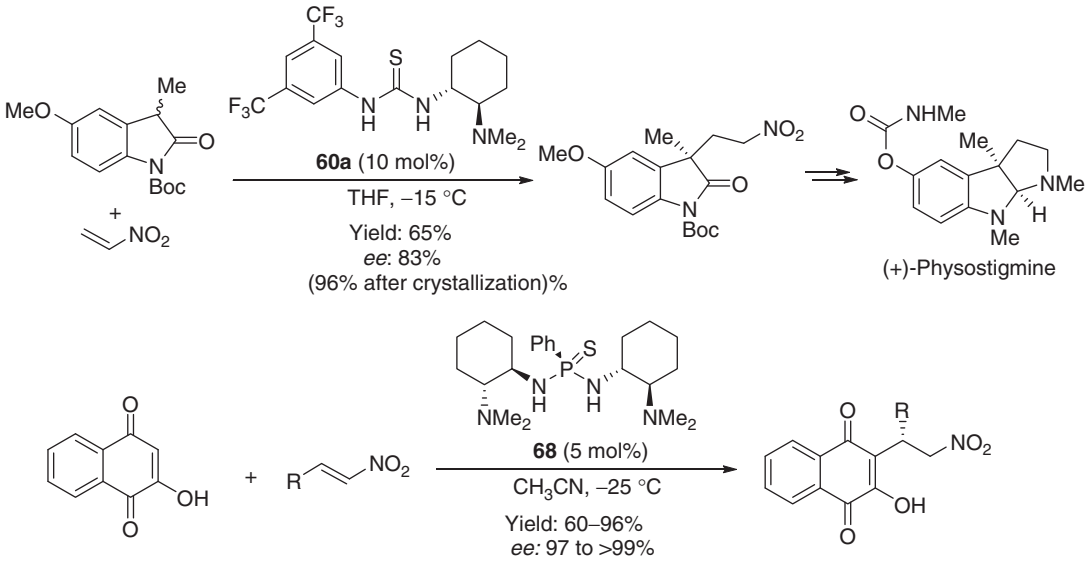
Scheme 30 Enantioselective Michael addition of malonates to nitroalkenes using **66a** and **40b** as catalysts.

Trying to carry out this reaction using nitroalkanes as Michael donors entails a very challenging situation because of the chemoselectivity issues arising due to the presence of two nitro compounds in the reaction scheme. In this case, the catalyst has to incorporate one H-bonding donor site, which has to differentiate clearly between both reagents, activating only the Michael acceptor and it is also desirable that it contains another secondary functionality that engages selectively on an additional interaction with the nitroalkane Michael donor. An illustrative example can be found in the case of the **67**-catalyzed Michael reaction of nitropropane and nitrobutane with nitrostyrenes, leading to the generation of adducts with two contiguous stereogenic centers in good yields and diastereo- and enantioselectivities (Scheme 31).[173] This BINOL-based catalyst contains an aminopyridine moiety that is able to participate selectively in the activation of the nitroalkane by assisting its deprotonation and also by stabilizing the formed nitronate via double H-bonding interactions and also incorporates a thiourea moiety, which activates the nitroalkene in the usual way. Other related bifunctional catalysts have also been tested in this transformation with different results.[174]



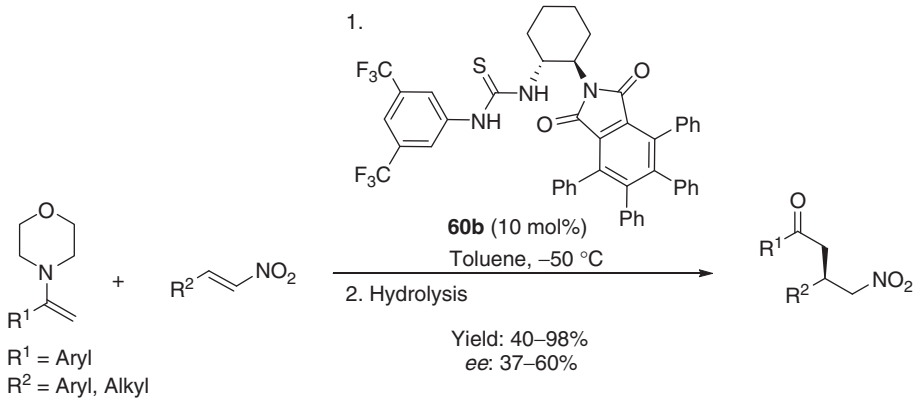
Scheme 31 Enantioselective Michael addition of nitroalkanes to nitroalkenes.

The search toward the identification of other C–H acidic compounds, which are able to participate as pronucleophiles in this reaction has also been intense, and, in this sense, several bifunctional tertiary amine/thiourea catalysts with different structures have been successfully employed in the Michael reaction of nitroalkenes with oxazolones,[175] dioxolan-4-ones,[176] anthracenones,[177] or 3-alkyl oxindoles.[178] The latter case constitutes a very good and representative example of the capacities of this methodologies to be used as crucial steps in the total synthesis of complex natural compounds, as can be seen from Scheme 32 showing the application of this methodology to the enantioselective formal total synthesis of the natural product (+)-physostigmine. In a different report, a modified thiophosphorodiamide version of Takemotós catalyst (**68**) has been employed in the Michael reaction of 2-hydroxy-1,4-naphtoquinone to nitroalkenes, which also shows that this type of compound is also suitable to be used in this transformation under the convenient activation by a bifunctional catalyst (Scheme 32).[179]



Scheme 32 Enantioselective Michael addition of 3-alkyl oxindoles and 2-hydroxy-1,4-naphtoquinone to nitroalkenes.

Finally, it should also be remembered that enolizable aldehydes or ketones have also been employed as Michael donors in the reaction with nitroalkenes using bifunctional primary or secondary amine/thiourea catalysts, although, these were considered in a previous section (see for example Figure 4) because, as pointed out at that moment, it was considered that this thiourea-nitroalkene interaction played a secondary role compared with the need for the activation of the Michael donor in the form of the corresponding enamine. Nevertheless, there is also an example reporting the addition of preformed enamines to nitroalkenes catalyzed by simple thiourea catalysts in which several morpholine enamines derived from aryl methyl ketones were reacted with both aliphatic and aromatic nitroalkenes in the presence of catalyst **60b** furnishing the corresponding γ-nitroketones after hydrolytic workup, in good yields although with moderate enantioselectivities (Scheme 33).[180]

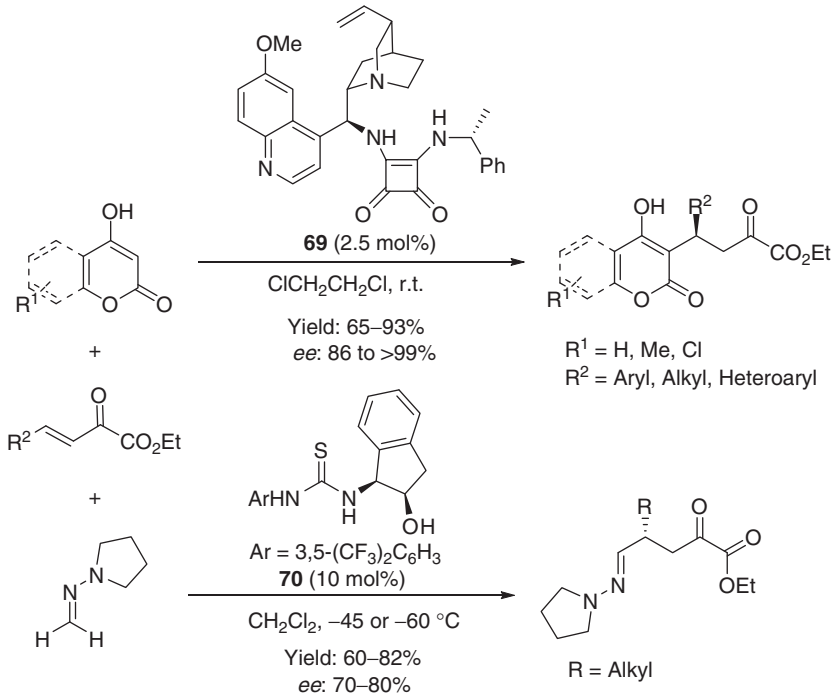


Scheme 33 Enantioselective Michael addition of enamines to nitroalkenes catalyzed by **60b**.

4.03.2.3.2 Enones and α,β-unsaturated aldehydes as Michael acceptors

The close electronic and structural similarities between α-oxo-β,γ-unsaturated esters and nitroalkenes allow the former to play the role of outstanding electrophilic substrates to undergo Michael reaction with a variety of carbon nucleophiles using bifunctional

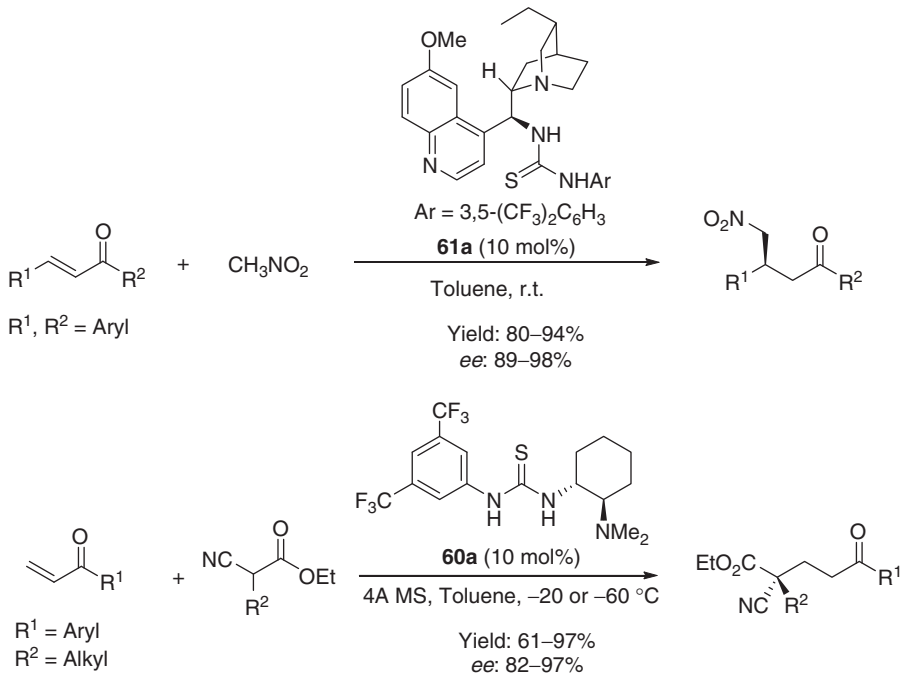
Bronsted base/H-bonding catalysis. A representative example illustrating this behavior is shown in Scheme 34, which comprises the use of 4-hydroxycoumarins and 4-hydroxypyrones as Michael donors in the presence of tertiary amine/squaramide catalyst **69**.[181] In addition, there is a noteworthy example of a Michael reaction in which *N*,*N*-dialkylhydrazones are employed as carbon nucleophiles undergoing conjugate addition to β,γ-unsaturated-α-ketoester using a bifunctional thiourea as catalyst.[182] These hydrazones can, therefore, be considered as masked formyl anion equivalents, which allow the preparation of 1,4-dicarbonyl compounds after the Michael reaction followed by hydrolysis of the hydrazone moiety. The key for the success of the reaction relied on the double Brønsted acidic character of the catalyst **70**, which is able to engage in simultaneous H-bonding interactions with both the Michael acceptor and the hydrazone reagent.



Scheme 34 Two examples of enantioselective Michael addition reactions to α-oxo-β,γ-unsaturated esters.

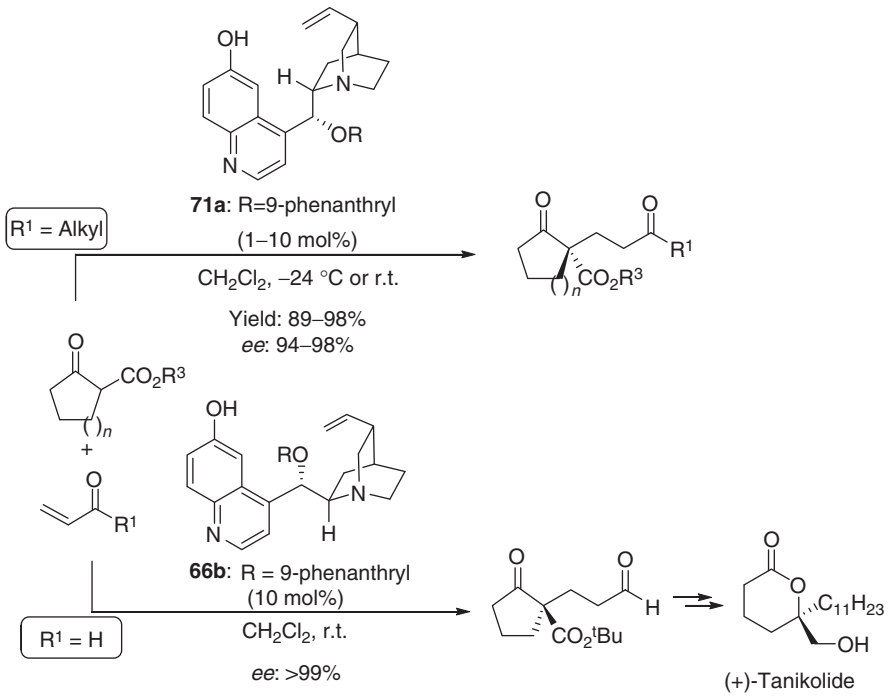
However, activating a simple enone toward a conjugate addition reaction through H-bonding interactions entails a more difficult situation compared with the use of this α-oxo-β,γ-unsaturated esters or nitroalkenes because of the lower Lewis basicity of the carbonyl group in enones compared with that of the nitro group and also because of the fact that enones can only participate in H-bonding interactions with the catalyst using a single oxygen atom, in contrast to the two oxygen atoms involved in the activation of nitroalkenes. Despite this, bifunctional thiourea-tertiary amine catalysts have also been found to be very convenient compounds for the activation of enones in Michael reactions because of their ability to engage in the formation of a double H-bonding network in which both lone pairs at the oxygen atom participate with the two H-donor sites of the catalyst. This leads to a very effective activation of the enone electrophile, and also to the formation of a well-defined tridimensional arrangement in the transition state. The first example reported in this context was related to the conjugate addition of nitromethane to chalcones developed by Soós using quinine-based thiourea catalyst **61a** (Scheme 35), in which the bifunctional nature of the catalysis is again crucial for achieving good yields and enantioselectivities, the basic quinuclidine moiety being involved in the activation of the pronucleophile in addition to the electrophile activation through the formation of the aforementioned H-bond network.[183] This type of catalyst has also been extended to other 1,3-dicarbonyl compounds and related derivatives such as malonates, malononitriles, β-ketoesters, 2,4-pentanedione, ethyl nitroacetate, anthrone, γ-butyrolactams, and cyanoacetates, which undergo an efficient and highly stereoselective Michael reaction with chalcones.[184] In different works, catalyst **60a** has been employed in several examples of Michael reactions using different types of Michael donors.[185] Scheme 35 shows a representative example in which the Michael reaction of α-substituted cyanoacetates to aryl vinyl ketones takes place with efficiency, leading to the formation of a quaternary stereocenter at the γ-position with respect to the ketone carbonyl group of the Michael acceptor.[186]

Alternatively, simpler cinchona alkaloids like **71a** have also been shown to constitute outstanding catalysts in the Michael addition of β-ketoesters to alkyl vinyl ketones (Scheme 36).[187] In this case, though the basic quinuclidine nucleus is still proposed to be involved in the activation of the Michael donor, the enone is supposed to be activated through the formation of a single H-bond between the phenolic moiety and the carbonyl group. The reaction was also shown to be fairly general regarding the use



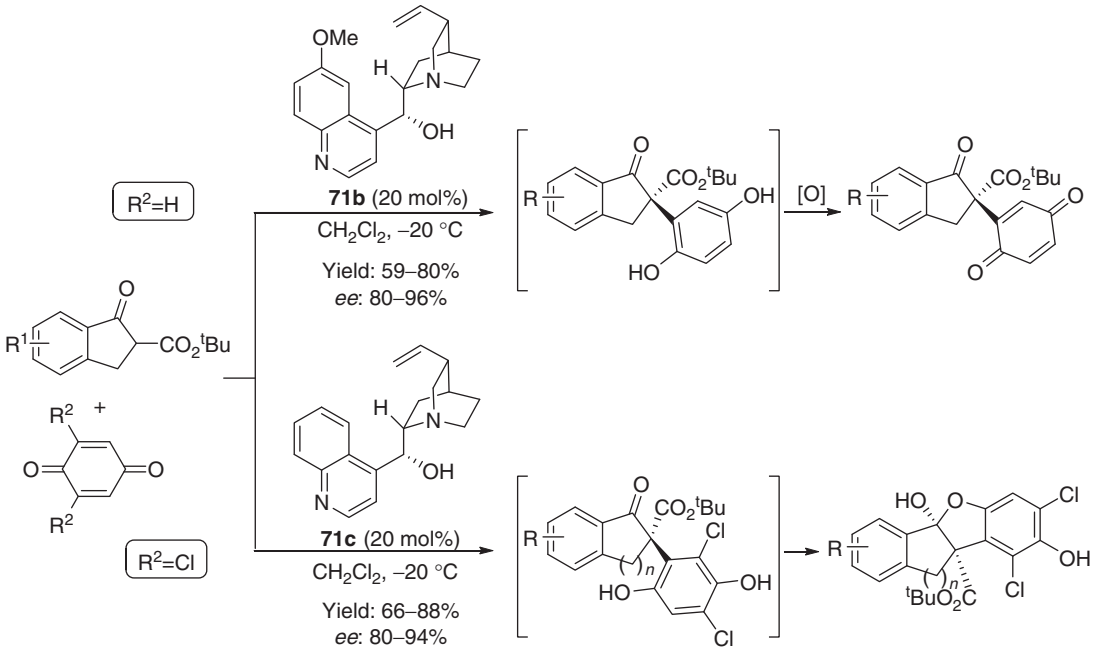
Scheme 35 Enantioselective Michael reactions with chalcones catalyzed by chiral thioureas.

of different cyclic and acyclic β-ketoesters of variable structures and also with regard to substitution at the vinyl ketone Michael acceptor. In addition, cyclic enones were also successfully tested in the reaction. These conditions can also be extended to the use of α,β-unsaturated aldehydes as Michael acceptors, using in this case the pseudoenantiomeric quinidine-based compound such as **66b** as the most effective catalyst for the reaction (Scheme 36).[188] Moreover, applicability of this methodology in the preparation of valuable compounds was also demonstrated with a short and efficient total synthesis of the natural product (+)-tanikolide, using this reaction as the key step in the synthesis.



Scheme 36 Enantioselective Michael addition of β-ketoesters to vinyl ketones catalyzed by cinchona alkaloids.

Quinones have also been surveyed as suitable Michael acceptors in the Michael reaction with β-ketoesters (Scheme 37). In this case, quinine **71b** was identified as the most efficient catalyst for this transformation but, interestingly, the 1,5-phenolic-type Michael adducts formed after the initial conjugate addition reaction underwent expontaneous oxidation by the presence of either atmospheric oxygen or excess quinone reagent, delivering a final quinone-type product.[189] This oxidation process was not observed when a quinone Michael acceptor incorporating electron-withdrawing substituents was employed, in which the aromatic diphenol moiety underwent intramolecular 1,2-addition to the β-ketoester residue, resulting in the stabilization of the Michael adduct as the related hemiacetal form. For this case, it was found that cinchonidine **71c** was a more efficient catalyst than quinine.



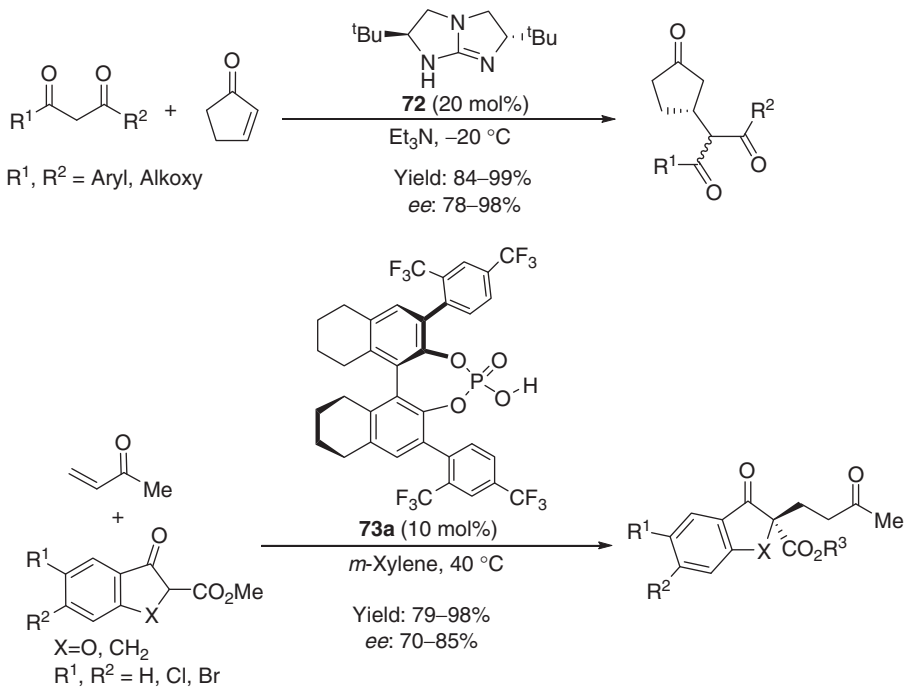
Scheme 37 Enantioselective Michael addition of β-ketoesters to quinones.

Other different structures capable of engaging in H-bonding interactions with enones have been employed as catalysts in this reaction by several research groups with success. For example, guanidines like **72** have been shown to perform well in the Michael reaction of different 1,3-dicarbonyl compounds with cyclopentenones,[190] and other acyclic enones[191] providing the final Michael adducts with excellent yields and enantioselectivities (Scheme 38). There is also one example in which a chiral phosphoric acid (**73a**) has been employed as the catalyst in the Michael reaction of cyclic β-ketoesters to methyl vinyl ketone.[192] This type of strong chiral Brønsted acids incorporate an axially chiral backbone derived from BINOL and also incorporates bulky substituents at the 2′ position which are the mainly responsible for inducing steric bias on the enantiotopic faces of the Michael acceptor. αα-Diarylprolinols are also capable to catalyze the Michael reaction of malononitrile to chalcones with moderate enantioselectivities, showing that these simple β-amino alcohols derived from proline can also engage in H-bonding activation events.[193]

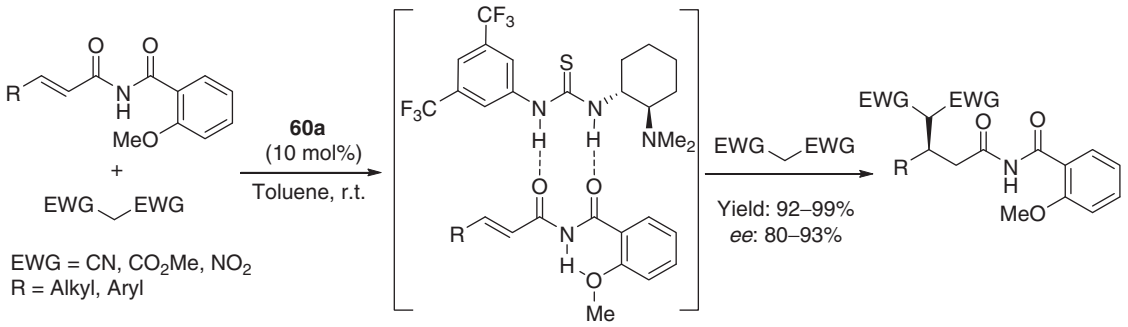
4.03.2.3.3 Other Michael acceptors

Other types of activated olefins have been employed as electrophilic reagents in Michael reactions with stabilized carbon nucleophiles under H-bonding activation. For example, the structural similarities between the imide and the nitro functionalities have been explored in several examples of conjugate addition reactions using a wide variety of C–H acidic pronucleophiles in the presence of catalyst **60a** (Scheme 39).[194] In this sense, the structure of the imide acceptor was crucial for achieving good results, especially in terms of conversion and reaction times and, in fact, α,β-unsaturated *o*-methoxybenzimides were identified as highly reactive electrophiles, allowing one to carry out the Michael reaction with malononitrile in a short reaction time and with high enantioselectivities. This higher reactivity was interpreted in terms of the possibility of stabilizing one conformer of the acceptor by intramolecular H-bonding between the NH group of the imide and the methoxy substituents, which would lead to a decrease in the electron density at the nitrogen atom and would also favor a very convenient orientation of the substrate toward the formation of H-bonding interactions with the thiourea catalyst. The methodology was proved to be very general regarding the use of differently substituted β-alkyl and β-aryl α,β-unsaturated imides and also related to the possibility of employing other C–H acidic pronucleophiles.

Maleimides have also been explored as suitable Michael acceptors in this context. For example, the Michael addition of β-ketoesters and 1,3-diketones to this type of electron-poor alkenes has been reported to occur in a very efficient way using natural cinchona alkaloids such as quinine **71b** or the pseudoenantiomeric quinidine as catalysts (Scheme 40).[195] The reaction yielded a

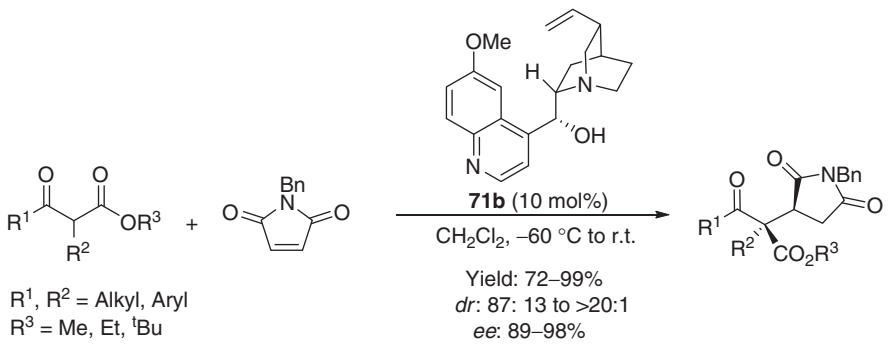


Scheme 38 Some examples regarding the use of guanidines and phosphoric acids as H-bonding catalysts for the enantioselective Michael reaction with enones.



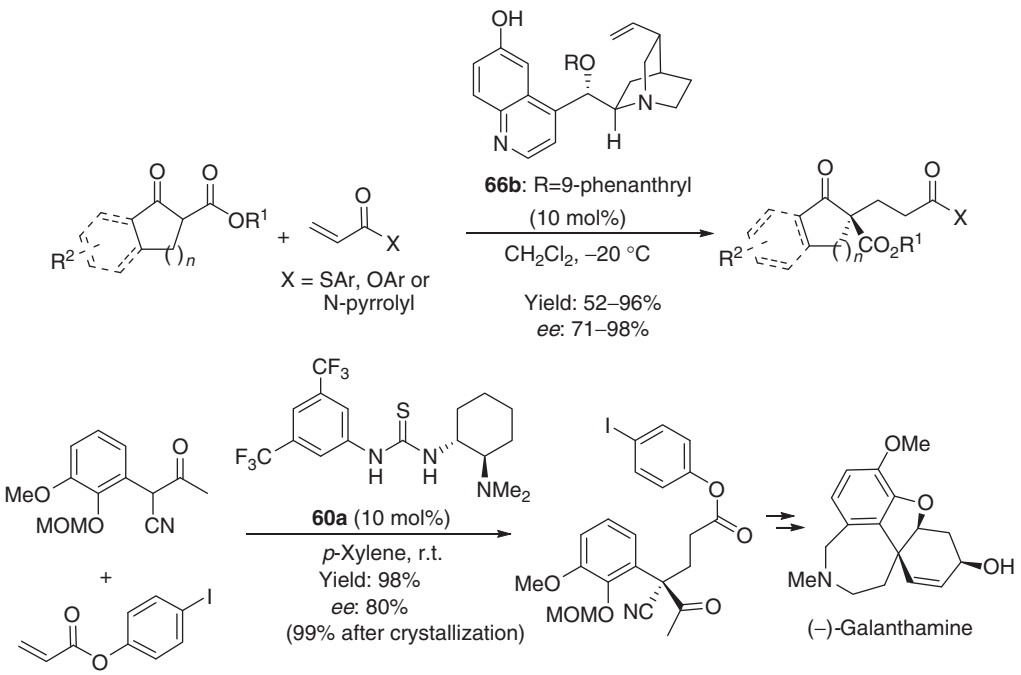
Scheme 39 **60a**-Catalyzed enantioselective Michael reactions using *N*-enoylimides as Michael acceptors.

family of products containing two stereogenic centers with excellent yields and diastereo- and enantioselectivities. Both enantiomers of the Michael adducts could be easily obtained using either quinine or quinidine. Similarly, other type of acidic carbon pronucleophiles have been surveyed in this transformation using other different catalysts, which were typically based on the cinchona alkaloid structure,[196] although other thioureas[197] and guanidines[198] have also been employed with success in some cases.



Scheme 40 Enantioselective Michael reaction of β-ketoesters with maleimide.

The use of acrylic acid derivatives or related compounds entails that the new stereocenter is always generated at the Michael donor moiety, which means that a conveniently substituted C–H pronucleophile has to be employed in order to generate a new stereogenic center. For this reason, most of the methodologies reported in this context involve the use of 2-substituted 1,3-dicarbonyl compounds or related derivatives as Michael donors. In this sense, the Michael reaction of β-ketoesters with different acrylic acid derivatives has been carried out using cinchona alkaloids like **66b** as the bifunctional catalysts in the presence of a base such as DABCO, required for the activation of the pronucleophile (Scheme 41), highlighting the possibility of using amides such as *N*-acryloyl pyrrole as Michael acceptors, which allowed the preparation of a variety of different compounds by carrying out chemoselective manipulations on the *N*-acylpyrrole moiety.[199] On the other hand, the Michael reaction of conveniently substituted α-aryl-α-cyanoacetates with acrylates has also been carried out in gram scale in the presence of several chiral tertiary amine/thiourea catalysts like **60a** or other cinchona-based thioureas. In this case, the corresponding conjugate addition products were obtained in quantitative yield albeit in moderate enantioselectivity, the latter parameter being improved by a single crystallization process. This potential for scale-up of this reaction has resulted in the application of this methodology as the key step in the enantioselective total synthesis of several natural products like (–)-galanthamine, (–)-lycoramine or (+)-lunarine.[200]

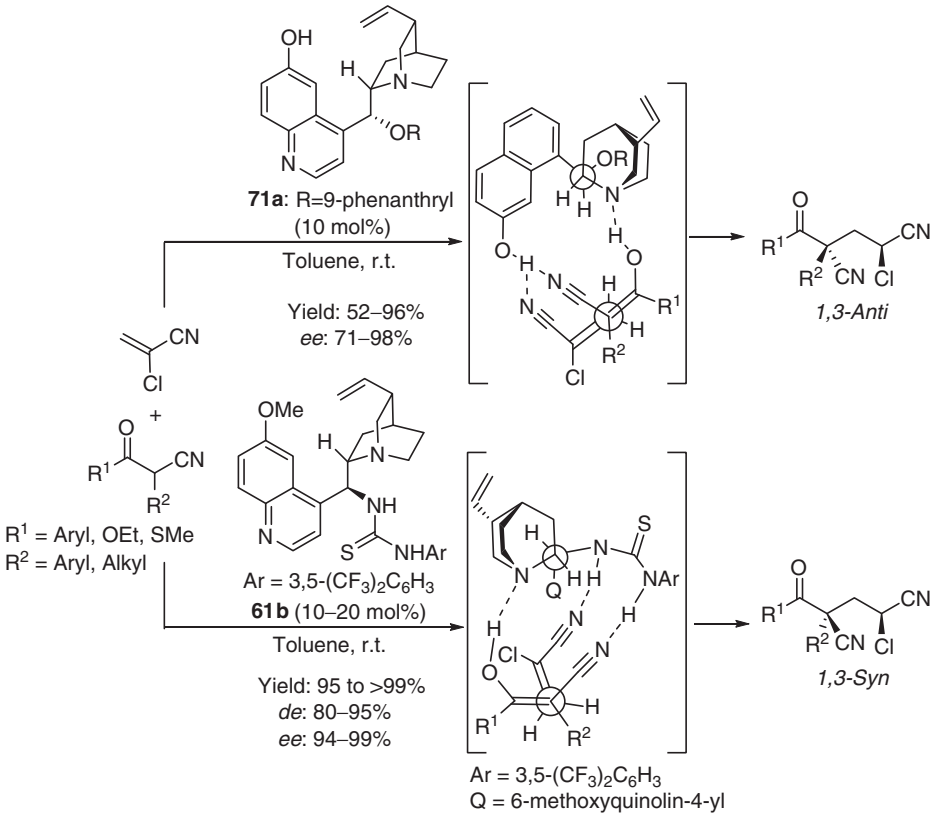


Scheme 41 Some exmaples of enantioselective Michael reactions to acrylic acid derivatives.

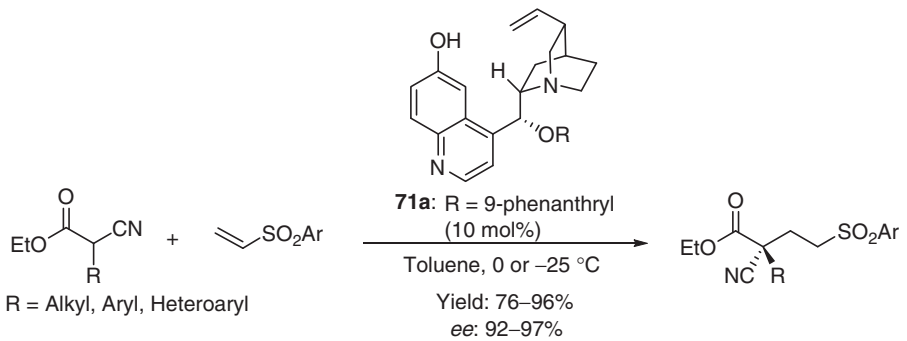
An interesting report has focused on the use of α-chlorocyanoacrylate as Michael acceptor, leading to the formation of adducts containing two stereogenic centers in 1,3-positions. In this case, catalyst **71a** was identified as an efficient promoter for the reaction which delivered the final compounds in good yields and in very high diastereo- and enantioselectivities (Scheme 42).[201] In addition, the authors also reported that changing to the related quinine-based thiourea catalyst **61b** allowed the preparation of the opposite 1,3-*syn* diastereoisomer. A model was provided to account for these results which was based on a catalyst-controlled intramolecular protonation of the intermediate formed after the conjugate addition step with the same sense of facial selectivity being the reason for obtaining the two different diastereoisomers in each case a matter of a difference in the sense of enantioinduction during initial Michael reaction for the two different catalysts.

Vinylsulfones have also been used as suitable Michael acceptors suitable to be activated by H-bonding interactions with a cinchone-type catalyst. In particular, **71a** was found to be an outstanding catalyst for the reaction of α-aryl-substituted cyanoacetates with vinyl sulfones, leading to the formation of highly functionalized chiral compounds containing a quaternary stereogenic center (Scheme 43).[202] Excellent yields and enantioselectivities were obtained for a wide range of different Michael donors tested. The structure of the vinyl sulfone reagent also played an important role in the reaction, observing that the use of less reactive or more sterically demanding β-alkyl-substituted cyanoacetates as Michael donors required a more electron-withdrawing sulfone functionality in order to reach full conversion. Chiral thioureas have also been employed as catalysts in the same reaction[203] and also in other related reactions which comprise the use of 1,1-bis(phenylsulfonyl)ethene,[204] vinyl bisphosphonates,[205] and α,β-unsaturated selenones[206] as Michael acceptors.

Finally, there is also one example of an intramolecular Michael reaction involving a nitroalkane as the Michael donor and a monoactivated α,β-unsaturated ester as the internal electrophile, which has been reported to proceed using



Scheme 42 Enantioselective Michael reactions of α-alkyl α-cyanoketones with α-chlorocyanoacrylate.

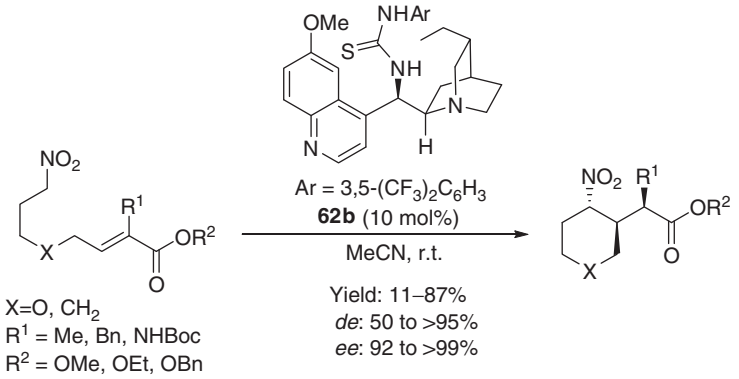


Scheme 43 Enantioselective Michael addition of α-alkyl α-cyanoketones to vinyl sulfones.

hydroquinidine-derived thiourea **62b** as the catalyst (Scheme 44).[207] The reaction furnished functionalized cyclohexanes and pyranes with moderate yields and diastereoselectivities but with excellent enantioselectivities for a variety of different substrates tested, which also include the possibility of employing highly sterically hindered α-substituted α,β-unsaturated ester-containing starting materials leading to the formation of an additional stereocenter at the α-position of the ester moiety.

4.03.2.4 Phase Transfer Catalysis

PTC has become a very powerful tool for achieving stereocontrol in conjugate addition reactions, with several methodologies and catalysts showing an excellent performance in some useful examples. In fact, PTC conditions are very convenient for this transformation because, in principle, almost any enolizable carbonyl compound can be employed as the Michael donor, due to the fact that the reaction scheme itself allows the introduction of an external base for the deprotonation of the pronucleophile. Nevertheless, it should be pointed out that the nature of the base employed for this purpose has to be carefully selected because it has to be strong enough to deprotonate the Michael donor but it must also be compatible with the presence of water. In this context, most methodologies have focused on the use of *N*-protected α-aminoesters (usually glycinate-benzophenone imines) as

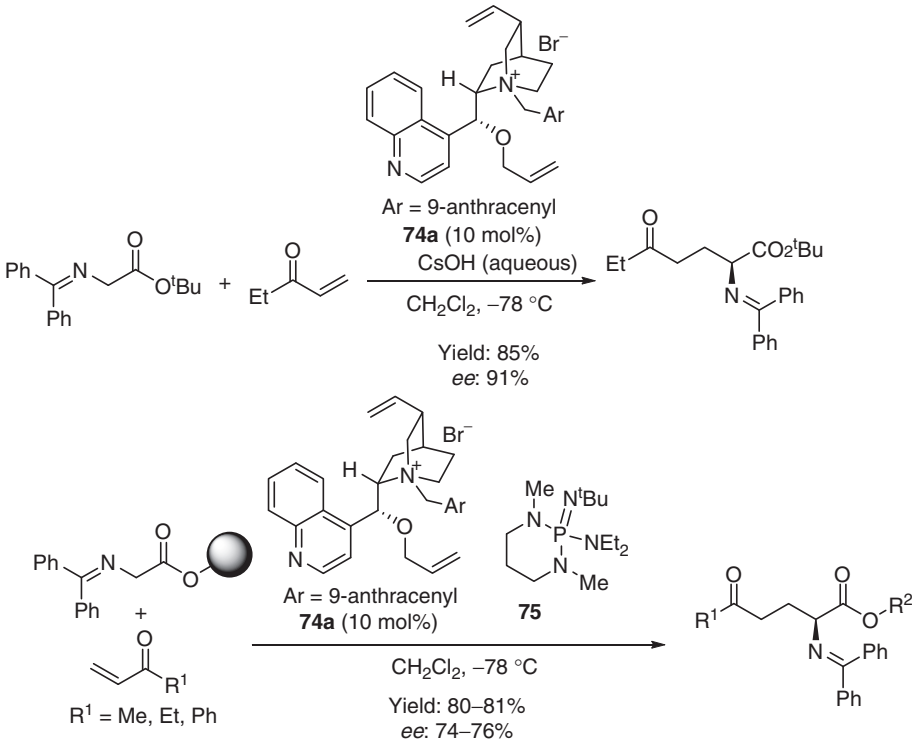


Scheme 44 Enantioselective intramolecular Michael reaction of 8-nitro-1-octenoates.

Michael donors, which incorporate an acidic enough α-H atom to undergo deprotonation using weak bases such as aqueous metal hydroxides or carbonates. Alternatively, the use of 1,3-dicarbonyl compounds or nitroalkanes as pronucleophiles has also been surveyed.

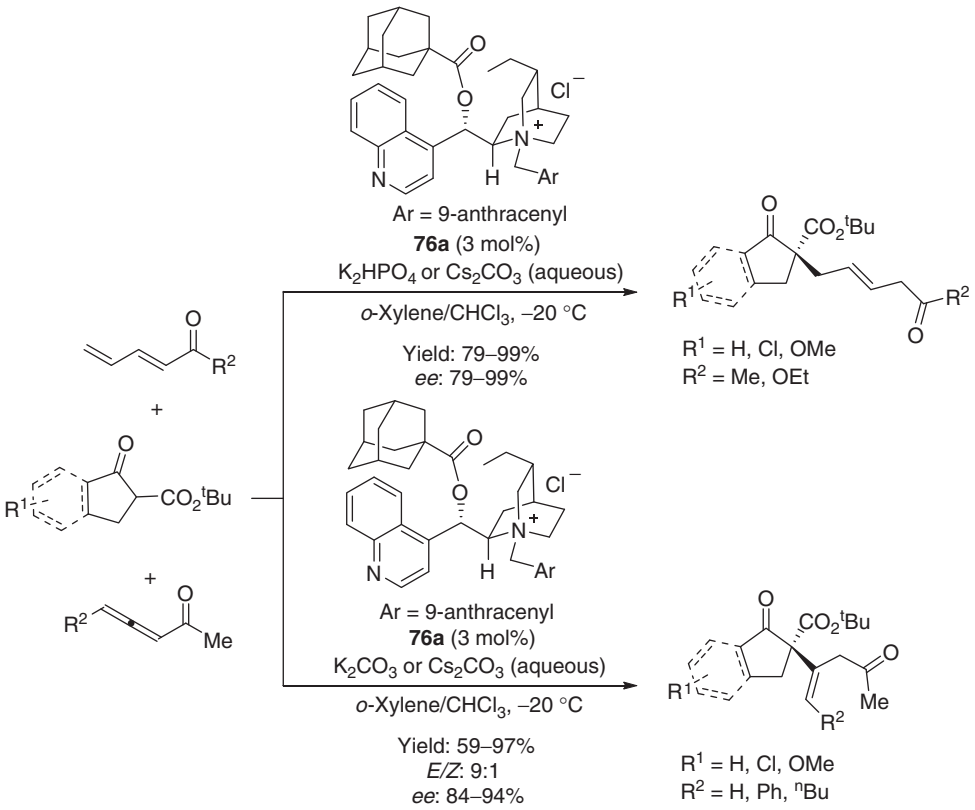
4.03.2.4.1 α,β-Unsaturated ketones and aldehydes as Michael acceptors

The conjugate addition of *tert*-butyl glycinate benzophenone imine to cyclohexanone and ethyl vinyl ketone was found to proceed with excellent yields and enantioselectivities, using cinchona-based chiral ammonium salt **74a** as catalyst (Scheme 45)[208] and incorporating cesium hydroxide as the most appropriate base to generate the reactive enolate species. This is a good example showing the appropriateness of the architecture of this type of chiral quaternary ammonium salts based on cinchona alklaloids for PTC, in which the quaternary quinuclidine nucleus engages in electrostatic interactions with the anionic nucleophile and the organic scaffold around the nitrogen cation ensures the required lipophilicity to be soluble in organic solvents. The same reaction can also be carried out in solution and in solid-phase using cinchonidine-based ammonium salt **74a** as the catalyst (Scheme 45),[209] requiring in this case the use of a nonionic organic phosphazene base **75**, which allowed a very effective *in-situ* generation of the enolate nucleophile. A chiral crown ether derived from glucose has also been developed as an efficient catalyst for this transformation.[210]



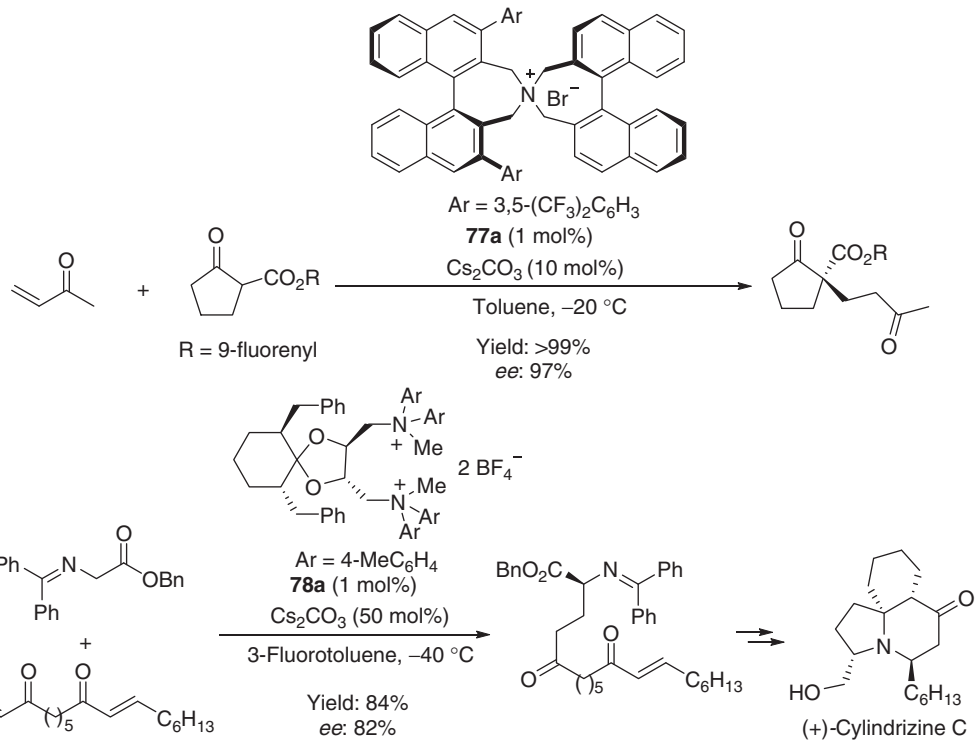
Scheme 45 Enantioselective Michael reaction of *tert*-butyl glycinate benzophenone imine with enones using cinchonidinium salts as PTC catalysts.

The use of this type of quaternary ammonium salts derived from cinchona alkaloids has been further extended to other acidic carbon pronucleophiles and, in this sense, structurally related catalysts have been successfully employed in the Michael reaction of enones with nitroalkanes,[211] malonates,[212] β-ketoesters,[213] or bis(phenylsulfonyl)methane[214] among others. Moreover, the behavior of polyunsaturated ketones as electrophiles has also been studied, observing that these type of Michael acceptors show a pronounced tendency to undergo 1,6-addition[215] rather than the usual 1,4-regioselectivity in the presence of several PTC catalysts among which *O*-adamantoyl-modified dihydrocinchonium derivative **76a** was identified as the most efficient one for this transformation (Scheme 46).[216] The reaction leads to a β,γ-unsaturated final product, which, in some exceptional cases can isomerize to the more stable conjugated enone. It has also to be noted that other different Michael acceptors such as $\alpha,\beta,\gamma,\delta$-unsaturated esters and sulfones were also employed with success in this reaction. Similarly, when allenic ketones are employed as Michael acceptors in the reaction with cyclic β-ketoesters, it takes place at the β-position of the allenone electrophile, also furnishing a β,γ-unsaturated ketone product and generating a quaternary stereogenic center.[217] Moreover, when γ-substituted allenes were employed, excellent diastereoselectivity control was also achieved regarding the geometry of the C=C double bond remaining at the final product, favoring the formation of the less sterically hindered *E* diastereoisomer. As it happened in the previous case, allenic esters were also employed with success in the same context.



Scheme 46 Enantioselective Michael reaction using $\alpha,\beta,\gamma,\delta$-unsaturated ketones under PTC conditions.

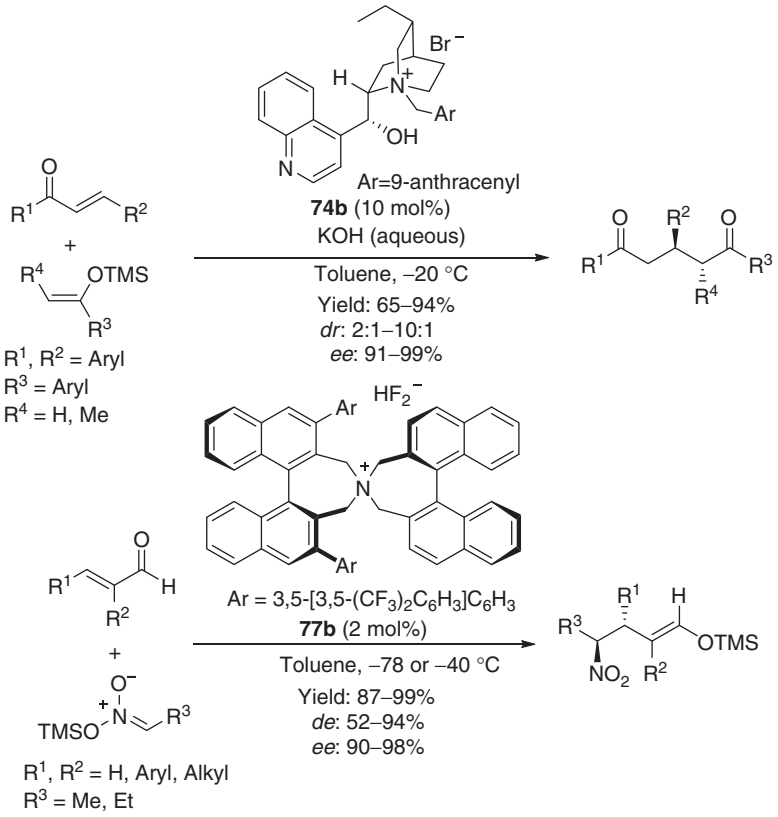
Other chiral ammonium salts based on different structural architectures have also been developed and, among them, the case of BINOL-based quaternary ammonium salts incorporating axial elements of chirality has been particularly effective in many different examples. For example, *N*-spiroammonium bromide **77a** incorporating an axially chiral binaphthyl backbone has been identified as an outstanding catalyst for the conjugate addition of a cyclic β-ketoester to methyl vinyl ketone, requiring the use of a fluorenyl ester as pronucleophile in order to obtain a high enantioselectivity (Scheme 47).[218] Other structurally related catalysts have been developed for promoting the Michael reaction of enones with nitroalkanes,[219] malonates,[220] α-cyanoacetates,[221] 1,3-dioxolan-4-ones,[222] or glycinate imines.[223] Importantly, α,β-unsaturated aldehydes, which are challenging substrates to be used as Michael acceptors under PTC conditions because of their tendency undergo self-condensation, were also found to be suitable substrates using this type of catalysts.[218] Alternatively, bis-ammonium salt **78a** has been expressly designed by Shibasaki for the conjugate addition of benzyl glycinate benzophenone imine to heptadec-1,10-dien-3,9-dione as the key step toward the enantioselective total synthesis of (+)-cilindrizine C (Scheme 47).[224] After extensive work, the authors found that an excellent yield and a synthetically useful 84% *ee* of the Michael adduct could be obtained using 10 mol% of **78a**, with Cs_2CO_3 as the base required for the activation of the nucleophile.



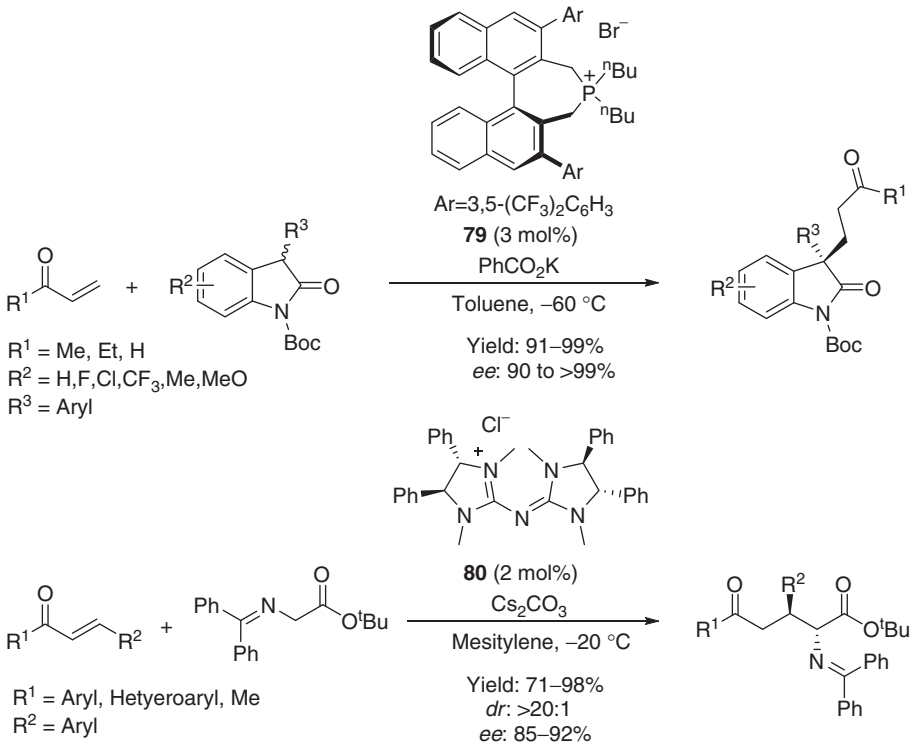
Scheme 47 Examples of enantioselective Michael reactions catalyzed by ammonium salts **77a** and **78a**.

The Mukaiyama–Michael approach is a very useful tool for performing Michael addition using compounds of lower acidity which cannot be deprotonated using weak bases such as those usually employed in PTC reactions and, for example, the conjugate addition of silyl enol ethers to chalcones can be carried out using **74b** as the catalyst.[225] As it is shown in Scheme 48, differently substituted chalcones can be used in this transformation as Michael acceptors, obtaining the final adducts with good-to-excellent yields and very high enantioselectivities. Moreover, α-substituted silyl enol ethers could also be employed as Michael donors, conducive to the formation of conjugate addition products containing two contiguous stereocenters and observing that, in this case, the reaction proceeded with very high diastereoselectivity, favoring the formation of the *anti* diastereoisomer and maintaining the excellent efficiency as observed in the same reactions with α-unsubstituted silyl enol ethers. An interesting variant has been reported in which enals are used as Michael acceptors in the reaction with silyl nitronates in the presence of fluoride ammonium salt **77b** (Scheme 48).[226] This catalyst, incorporated bulkier aryl substituents at the 2′-positions of the binaphthyl substructure compared with **77a** and also a bifluoride HF_2^- anion as a counterion was included, the latter required for the *in-situ* activation of the silyl nitronate reagent. Working under these typical Mukaiyama-Michael conditions, a variety of differently substituted nitronates and enals reacted with each other in a highly efficient manner, providing the corresponding conjugate addition products in excellent yields and enantioselectivities. More importantly, the use of α-alkyl-substituted nitronates led to the formation of products containing two contiguous stereogenic centers with excellent diastereoselectivity, overcoming the limitations typically associated with the enantioselective nitro-Michael reaction under Lewis acid catalysis. Moreover, α,β-disubstituted enals were also tested with success, leading to the formation of final products containing three contiguous stereocenters after acid hydrolysis with excellent results regarding both yields and stereoselectivities.

Finally, it should also be pointed out that enantioselective Michael reactions under PTC conditions do not exclusively rely on the use of chiral ammonium salts as catalysts and, for example, chiral phosphonium salts can also be successfully employed in this context. This is the case of binaphthyl-containing phosphonium salt **79**, which was demonstrated to be an outstanding catalyst in the conjugate addition of oxindoles to enones under PTC conditions (Scheme 49).[227] The Michael adducts were obtained in excellent yields and enantioselectivities for a wide variety of differently substituted 3-aryl oxindoles tested as Michael donors. Remarkably, the high acidity of the 3-aryloxindoles employed as Michael donors allowed the use of a very mild base such as potassium benzoate for the activation of the nucleophile. In a different report, chiral pentanidinium cation **80** has been recognized as a novel architecture for the design and development of a new type of PTC catalysts, which have demonstrated their outstanding performance in the Michael reaction between glycinate imines and acyclic enones.[228] An important novel feature associated with this type of catalyst is the fact that it contains an sp^2-quaternized ammonium salt entity, which stands in deep contrast with all previously presented examples in which typically an sp^3-hybridized quaternary ammonium salt forms the basis of the catalyst structure.



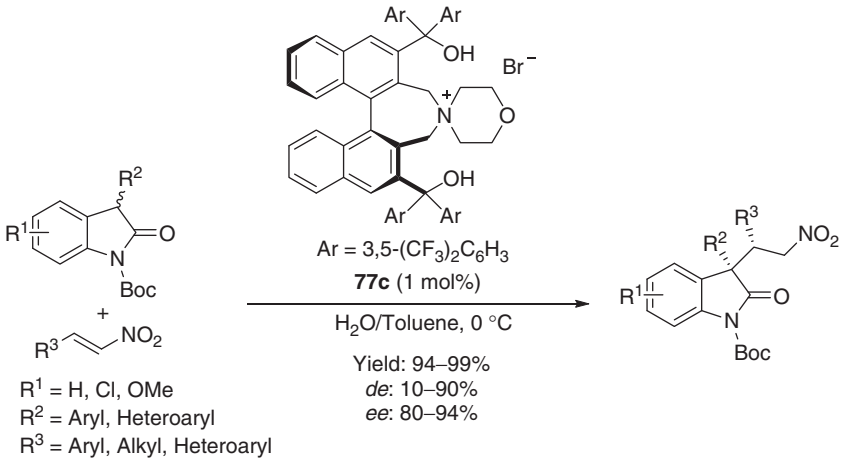
Scheme 48 Enantioselective Mukaiyama–Michael reaction under PTC conditions.



Scheme 49 Phosphonium and pentadinium salts as catalysts in enantioselective Michael reactions under PTC conditions.

4.03.2.4.2 Nitroalkenes as Michael acceptors

Nitroalkenes are challenging Michael acceptors to be used under PTC conditions because the high electrophilicity of these reagents makes the uncatalyzed background reaction to be competitive in this case. For this reason, the number of reports dealing with this particular set of reactions is very limited. There is one very remarkable example regarding the enantioselective Michael reaction of oxindoles with nitroalkenes under PTC conditions, which makes use of the ammonium salt catalyst **77c** (Scheme 50).[229] Deuterium labeling experiments showed that oxindoles underwent fast deprotonation in neutral aqueous media only in the presence of the catalyst, whereas they remained essentially unchanged when this catalyst was not present or when other quaternary ammonium salts were added. Under these conditions, the reaction of a variety of α-substituted oxindoles with a series of nitroolefins was found to occur smoothly in the presence of **77c**, furnishing the expected conjugate addition products in excellent yields and enantioselectivities. The diastereoselectiviy of the reaction was, however, found to be highly dependent on the nature of the α-substituent of the oxindole donor and on the β-substituent of the nitroalkene acceptor. The reaction also tolerated well the substitution at the nitroalkene reagent, allowing the use of both aromatic and aliphatic nitroalkenes with similar results. However, only α-aryl-substituted oxindoles could be used as Michael donors, observing very poor results with α-alkyl-substituted derivatives, probably due to the lower acidity of these compounds that underwent deprotonation very slowly under the reaction conditions employed. There is another example regarding the use of a monosaccaride-based chiral crown ether as the phase-transfer catalyst in the Michael reaction between aminomalonates and nitroalkenes proceeding with moderate yields and excellent enantioselectivities for a variety of nitrostyrenes.[230]

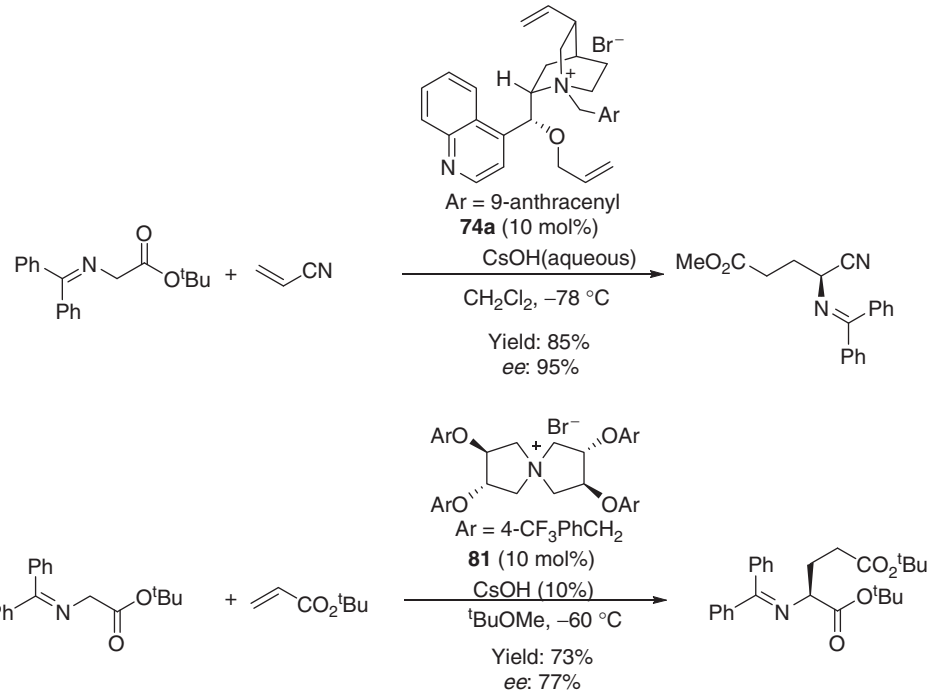


Scheme 50 Enantioselective Michael reaction of α-aryl oxindoles with nitroalkenes.

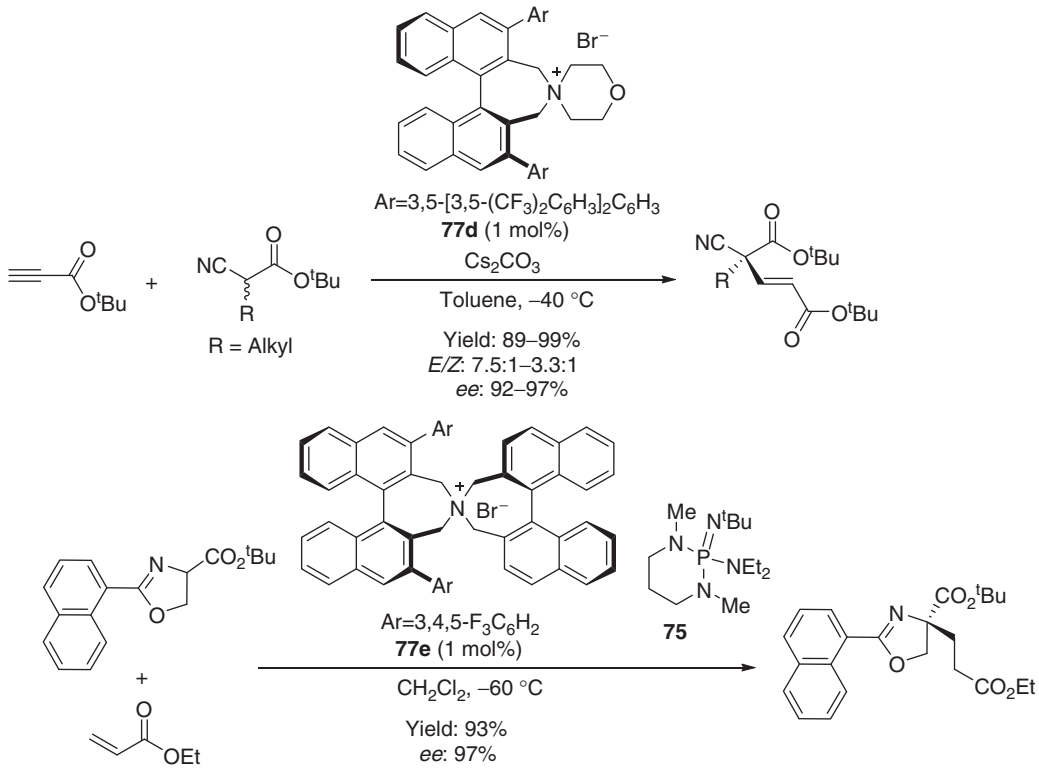
4.03.2.4.3 Acrylic acid derivatives as Michael acceptors

Almost all the catalysts presented up to this point have also been tested in the Michael reaction with acrylic acid derivatives, typically acrylate esters and acrylonitrile. For example, the addition of *tert*-butyl glycinate benzophenone imine to methyl acrylate had already been studied by Corey in 1998 in his first report on cinchonidinium salt **74a**-catalyzed enantioselective Michael reactions using enones as the Michael acceptors shown in Scheme 45.[208] Under the same reaction conditions, both methyl acrylate and acrylonitrile reacted efficiently, furnishing the final Michael adducts in excellent yields and enantioselectivities (Scheme 51).[231,232] Other chiral ammonium salts not derived from cinchona alkaloids have also been used in this context like tartaric acid-derived quaternary ammonium salt **81** having a spiroammonium functionality shown in Scheme 51, which performs well in the reaction of *tert*-butyl glycinate benzophenone imines with *tert*-butyl acrylate.[233] Several chiral crown ethers have also been used with different success rates in several cases of Michael reactions with methyl acrylate or acrylonitrile.[234]

On the other hand, axially chiral *N*-spiroammonium salt **77d** has been found to catalyze the Michael reaction of α-substituted cyanoacetates with acetylenic esters, providing the final adducts in almost quantitative yields and with excellent enantioselectivities (Scheme 52).[234] However, regarding the geometry control at the newly generated C=C double bond, the diastereoselectivities remained in moderate values, ranging from 7:1 to 2:1 *E*/*Z* ratios, favoring the more stable *E* diastereoisomer. Interestingly, the enantiomeric excesses observed for the minor *Z* diastereoisomers, when isolated, were found to be approximately 10% lower than those obtained in the corresponding *E* diastereoisomer. A similar catalyst **77e** has been employed in the Michael reaction of a serine nucleophile equivalent of ethyl acrylate (Scheme 52).[235] In this case, the researchers found that enantioselectivity was strongly dependent on the nature of the base used to deprotonate the substrate and, after extensive research, it was found that the final Michael adduct could be isolated in excellent yield and enantioselectivity using phosphazene base **75**. In addition, the aromatic group linked to the oxazoline moiety was also found to play an important role in the reaction, requiring the incorporation of a 1-napthyl substituent for achieving high yield and enantioselectivity.

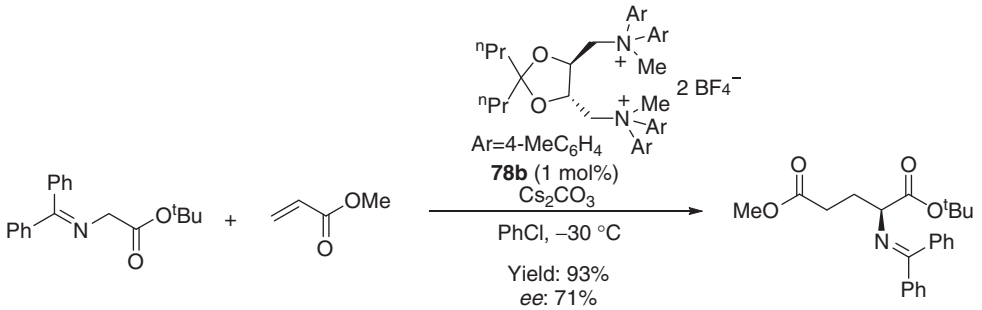


Scheme 51 Some examples of enantioselective Michael reactions of glycinate imines with acrylic acid derivatives.



Scheme 52

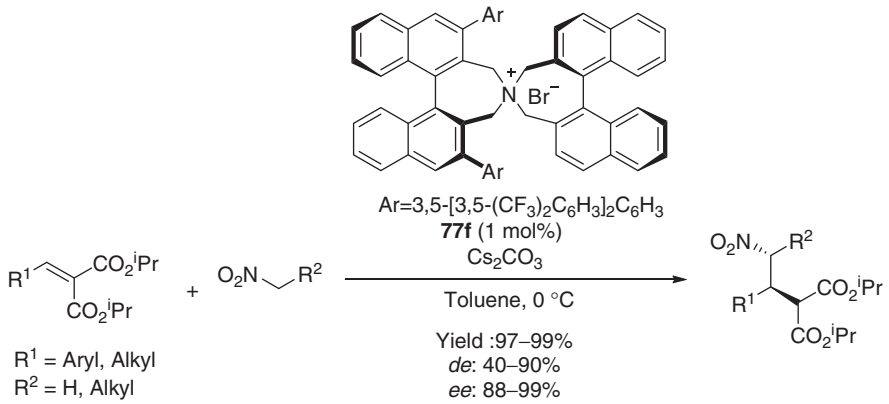
Finally, tartrate-derived quaternary ammonium salt **78b** has been demonstrated to perform very well in the Michael reaction of glycinate imines with acrylates (Scheme 53).[236] Remarkably, the presence of two quaternary ammonium salt moieties on the catalyst structure was revealed to be crucial for achieving good stereoselection, observing that when other families of related catalysts containing a single quaternary ammonium center were tested the Michael adduct was obtained in very low *ee*. The nature of the anionic counterion was also important, obtaining the best results with the bis-trifluoroborate salt.



Scheme 53 Enantioselective Michael reaction of *tert*-butyl glycinate benzophenone imine with methyl acrylate catalyzed by TADDOL-based ammonium salts.

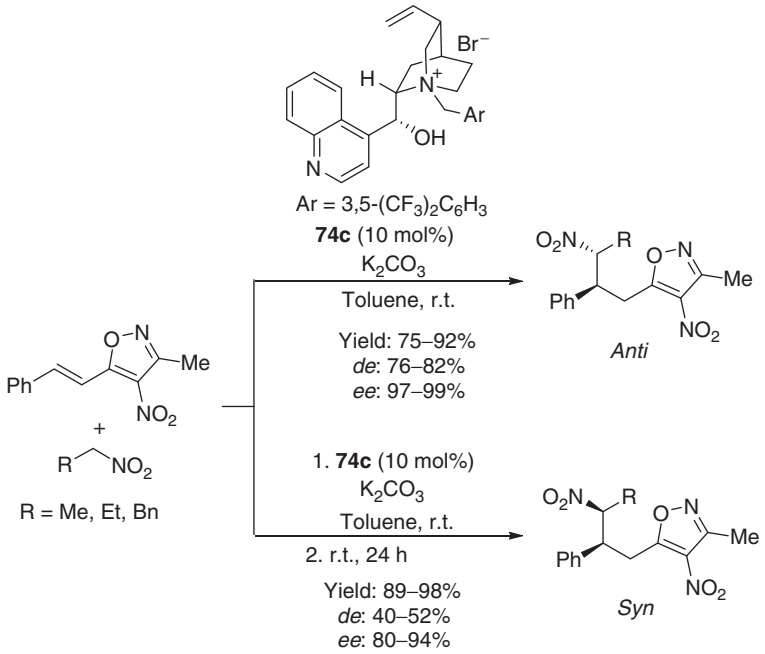
4.03.2.4.4 Other Michael acceptors

Some other activated olefins have been employed as acceptors in Michael reactions under PTC conditions. This is the case of vinylsulfones, which have been employed as Michael acceptors in the reaction with glycine imines using cinchonidinium salt **74a** as the catalyst both in solution or in solid-supported version and furnishing similar results as those provided by the corresponding vinyl ketones and acrylates.[209] However, *N*-spiroammonium bromide **77f** has also been successfully employed to catalyze the Michael reaction of nitroalkanes to alkylidenemalonates (Scheme 54),[237] leading to the corresponding conjugate addition products obtained in good yields although as mixtures of diastereoisomers in ratios ranging from 7:3 to 95:5, the *anti* isomer being the major one. In all cases, the enantioselectivity of the reaction was found to be excellent.



Scheme 54 Michael reaction of nitroalkanes with alkylidenemalonates catalyzed by **77f.**

Alternatively, conveniently substituted heterocyclic moieties can play the role of suitable electron-releasing groups for the activation of an olefin toward conjugate addition and, in particular 4-nitro-5-styrylisoxazoles were found to undergo clean and smooth addition with nitroalkanes in the presence of cinchonidine-based ammonium salt **74c** as catalyst (Scheme 55).[238] In addition, the nitroisoxazole heterocycle could be very easily converted into a carboxylic group by simple hydrolytic treatment. Moreover, the use of nitroalkenes other than nitromethane led to the formation of Michael adducts incorporating a second stereogenic center with similar high yields and enantioselectivities than those observed when nitromethane was employed, and it was also observed that the reaction proceeded with a very high degree of *anti*-diastereoselection. Interestingly, researchers were also able to obtain the corresponding *syn* diastereoisomer by a simple modification of the experimental procedure, which consisted of allowing the products to undergo *in-situ* epimerization promoted by the basic reaction medium by prolonging the reaction time which favored the formation of the more stable *syn* diastereoisomers.



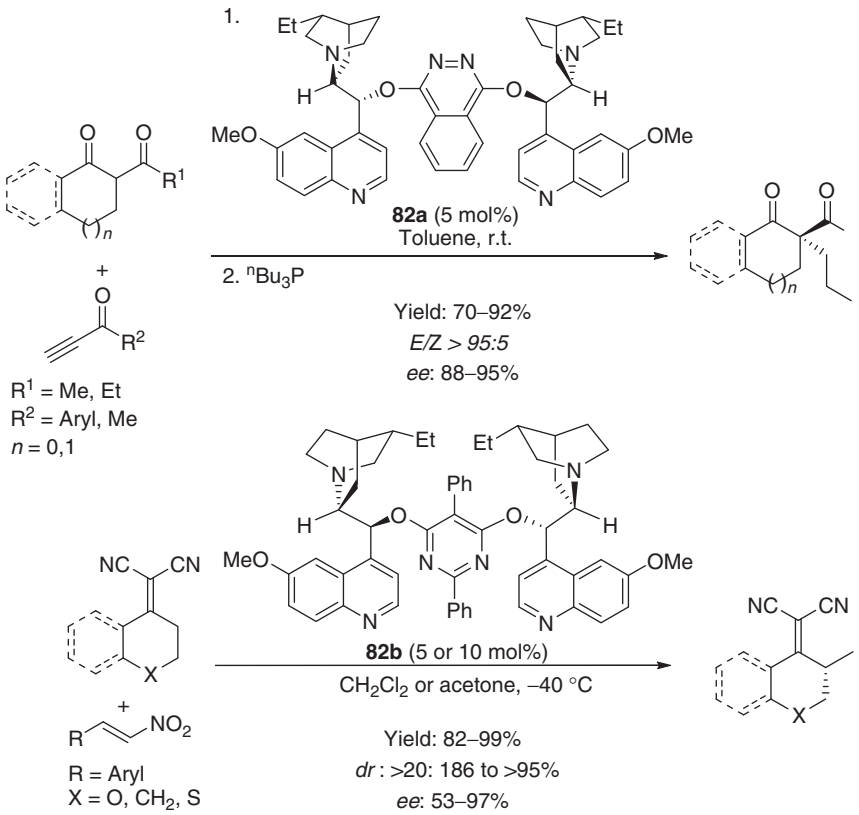
Scheme 55 PTC catalysis in the enantioselective Michael reaction using 4-nitro-5-styrylisoxazoles as Michael acceptors.

4.03.2.5 Bronsted Base Catalysis

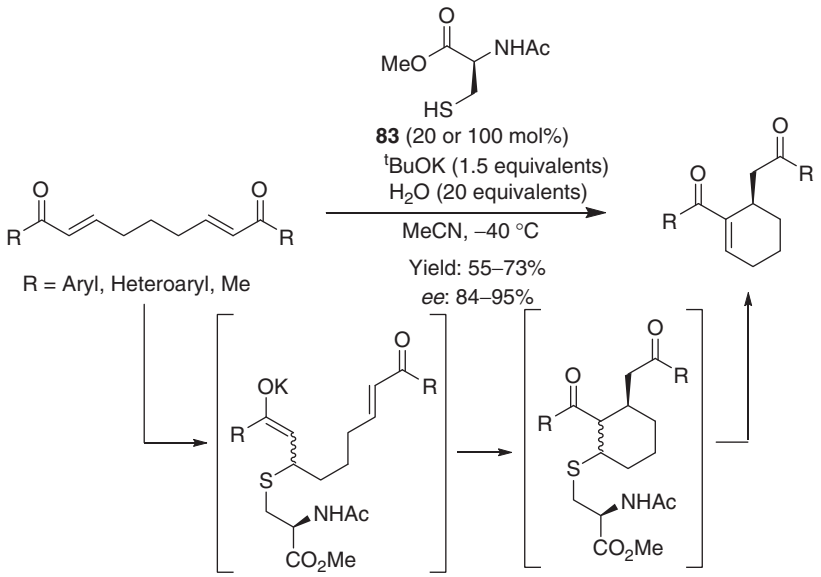
The use of chiral tertiary amines as bases for catalyzing the Michael reaction has not received so much attention as other organocatalytic activation manifolds, although it should be pointed out that participation of chiral Bronsted basic sites present in the structure of a bifunctional catalyst is very often found in the literature, and those cases are already covered in the previous sections. Nevertheless, several relevant examples exist in which simpler tertiary amine bases are employed as monofunctional catalysts without the presence of secondary functionalities that engage in other types of interactions with the substrates like, for example, H-bond donor sites. This is the case of dimeric cinchona alkaloid-based compounds like the one shown in Scheme 56 (**82a**), which is able to catalyze the Michael reaction of 2-alkyl-substituted 1,3-diketones with alkynones.[239] This type of catalyst incorporates multiple Bronsted basic sites in their structure capable to interact with the substrates participating in the reaction, generating a chiral environment for the reaction to proceed stereoselectively. Importantly, this reaction not only generates a quaternary stereocenter but also delivers a highly functionalized final product containing an $\alpha\beta$-unsaturated ketone side chain, suitable for further transformations. The reaction proceeded with good enantioselectivity but providing the final products as a mixture of *E* and *Z* isomers which were submitted to *in-situ* isomerization by addition of a catalytic amount of $n\text{Bu}_3\text{P}$, furnishing exclusively the *E* diastereoisomers. In a different context, a vinylogous conjugate addition reaction using alkenylmalononitriles as Michael donors and nitroalkenes as acceptors has been reported using the same type of chiral Bronsted base catalyst (Scheme 56).[240] The final products were obtained with excellent yields, diastereo- and enantioselectivities, and with the formation of regioisomers arising from the competitive possible reaction though the α-carbon of the nucleophile was not observed. Later on, the same strategy was applied to the use of quinones as Michael acceptors.[241]

4.03.2.6 Other types of Organocatalysts

The rich reactivity profile of activated olefins and nucleophiles participating in a conjugate addition reaction opens the way for multiple approaches in which an organic molecule can activate either the Michael donor or the acceptor. One representative example is the process known as Rauhut–Currier reaction in which one α,β-unsaturated carbonyl compound participates as Michael donor after undergoing reversible conjugate addition with the catalyst, releasing an enolate-type intermediate which subsequently proceeds to react with the Michael acceptor and finally the catalyst is released by means of the reversible nature of the initial conjugate addition step. In this context, *N*-protected cysteine **83** has been found to be an excellent promoter for the intramolecular Rauhut–Currier reaction shown in Scheme 57,[242] in which the catalyst activates of the enone which has to play the role of the Michael donor via sulfa-Michael addition. It should be pointed out that the catalyst required activation by deprotonation of the SH group by one equivalent of an external base additive (^{t}BuOK) and also that the reaction was carried out in most cases using stoichiometric amounts of promoter **83**, although in some cases the reaction was found to proceed satisfactorily using a 20 mol% of the catalyst. The reaction was tested on a variety of symmetrical bis-enone substrates, furnishing the final cyclohexenone products with excellent yields and enantioselectivities.



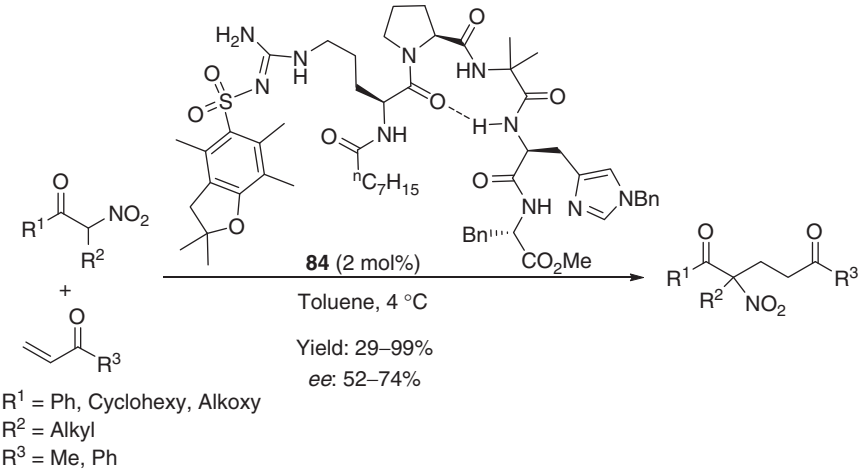
Scheme 56 Two examples of enantioselective Michael reactions catalyzed by Brønsted bases.



Scheme 57 Enantioselective intramolecular Rauhut–Currier reaction catalyzed by *N*-acetyl cysteine.

Small peptides can also promote several organic reactions in a stereoselective way[243] and with regard to the Michael reaction, in most of the cases, the peptide participates in the catalytic cycle by some of the previously covered activation modes, like enamine or iminium catalysis or additionally by activating the Michael acceptor by H-bonding interactions. However, there are some other examples in which a small peptide has been proposed to catalyze a conjugate addition reaction in which the activation mechanism involves the stabilization of a particular conformation of the peptide, which therefore could generate a chiral pocket in which the reagents participating in the reaction are incorporated. A good example is shown in Scheme 58, in which modified

peptide **84** was identified as the best catalyst for the Michael reaction of α-nitro ketones with enones among a wide variety of different peptides tested (Scheme 58).[244] This catalyst furnished the final Michael adducts with moderate enantioselectivities, albeit in good yields in many cases.



Scheme 58 Enantioselective Michael reaction of α-nitroketones with enones catalyzed by a small peptide.

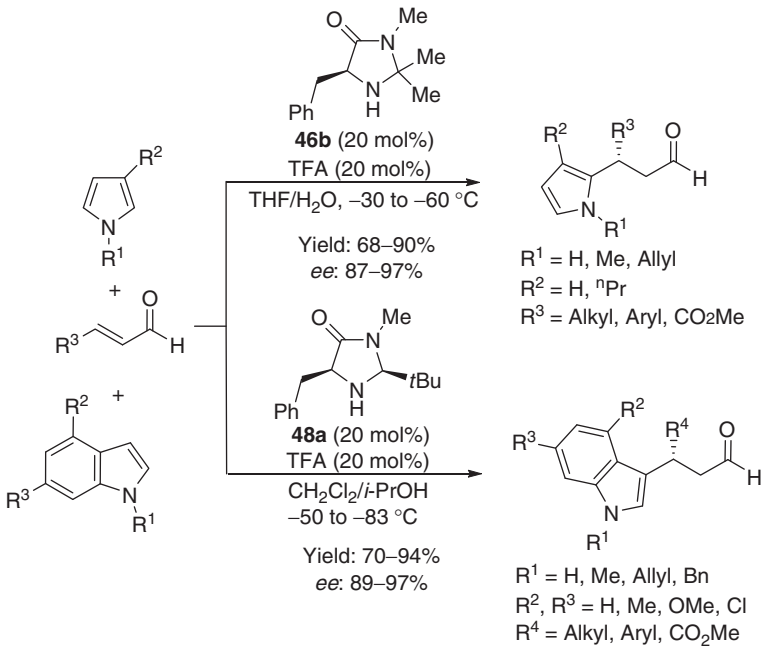
4.03.3 Conjugate Friedel-Crafts Alkylation

The conjugate addition of electron-rich aromatic compounds to α,β-unsaturated carbonyl compounds or related substrates is a powerful strategy for building up of complex heterocyclic structures. In this context, several organocatalytic variants for this transformation have been reported in the past few years,[245] focused especially on the activation of the Michael acceptor by iminium ion formation or by hydrogen-bonding interactions.

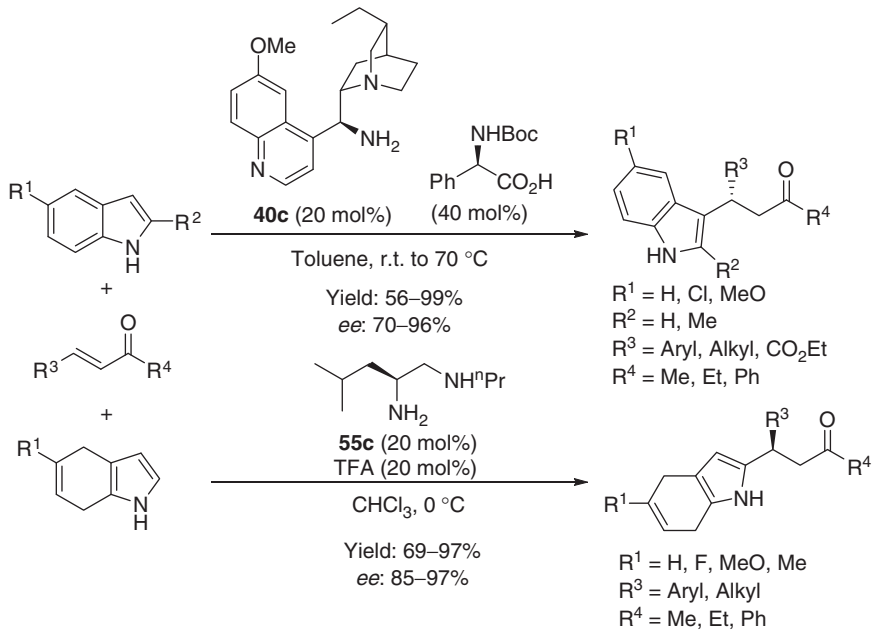
4.03.3.1 Iminium Catalysis

The application of iminium catalysis to the conjugate Friedel–Crafts alkylation has represented a breakthrough in this area due to the true complementarity between this approach and the standard enantioselective versions involving transition metal catalysis in the sense that iminium catalysis allows carrying out this transformation employing simple enones or α,β-unsaturated aldehydes as Michael acceptors, which cannot be used under Lewis acid catalysis because of their tendency to undergo 1,2-addition rather than conjugate addition. In this context, chiral imidazolidinones have been found to be outstanding catalysts for the reaction between several electron-rich aromatic systems and enals. In particular, heterocycles with highly nucleophillic character such as pyrroles underwent a smooth reaction using catalyst **43b**,[246] whereas applying the same conditions to heteroaromatics of significantly lower reactivity such as indoles required the use of modified imidazolidinone **48a**. In this new catalyst, one of the methyl groups of the imidazolidinone moiety was substituted by a smaller hydrogen atom in order to favor the condensation of the catalyst with the enal reagent and, in addition, a *tert*-butyl group was introduced in place of the other methyl group, which was supposed to increase the capacity of the catalyst to stereodiscriminate between the faces of the Michael acceptor.[247] This new design, also referred to as the second generation MacMillan catalyst, also proved to be extremely effective in the addition of electron-rich benzenes to α,β-unsaturated aldehydes (Scheme 59).[248] Several modified analogs of these imidazolidinone catalysts have also demonstrated their ability in this reaction[249] and also other catalysts, not based in the imidazolidinone skeleton have been developed for the conjugate Friedel-Crafts alkylation of indoles and 4,7-dihydroindoles with α,β-unsaturated aldehydes.[250] Moreover, different intramolecular variants have been developed for the formation of fused aromatic and heteroaromatic compounds in a very efficient and stereoselective way.[251]

This type of MacMillan-type imidazolidinones have also been applied to the use of enones as Michael acceptors but with moderate results,[252] which has led to the use of primary amines as more appropriate catalysts when activation of these substrates is required. In fact, hydroquinine-based derivative **40c** in combination with a chiral amino acid as the Brønsted acid cocatalyst has shown to catalyze the reaction between indoles and a wide range of different acyclic enones, obtaining the corresponding adducts in good-to-moderate yields and enantioselectivities (Scheme 60).[253] Alternatively, a much more structurally simple catalyst such as diamine **55c** was found to perform very well in the reaction between 4,7-dihydroindoles and several enones.[254] In this case, the catalyst is proposed to participate as a bifunctional entity in which in addition to the ability of the primary amine moiety to activate the Michael acceptor through iminium ion formation, the secondary amine functionality is proposed to engage in H-bonding interactions with the indole reagent, which was supported by the fact that the corresponding modified *N*-methyl dihydroindole substrate was found to be inactive in the reaction.



Scheme 59 Chiral imidazolidinone-catalyzed enantioselective conjugate Friedel-Crafts alkylations.

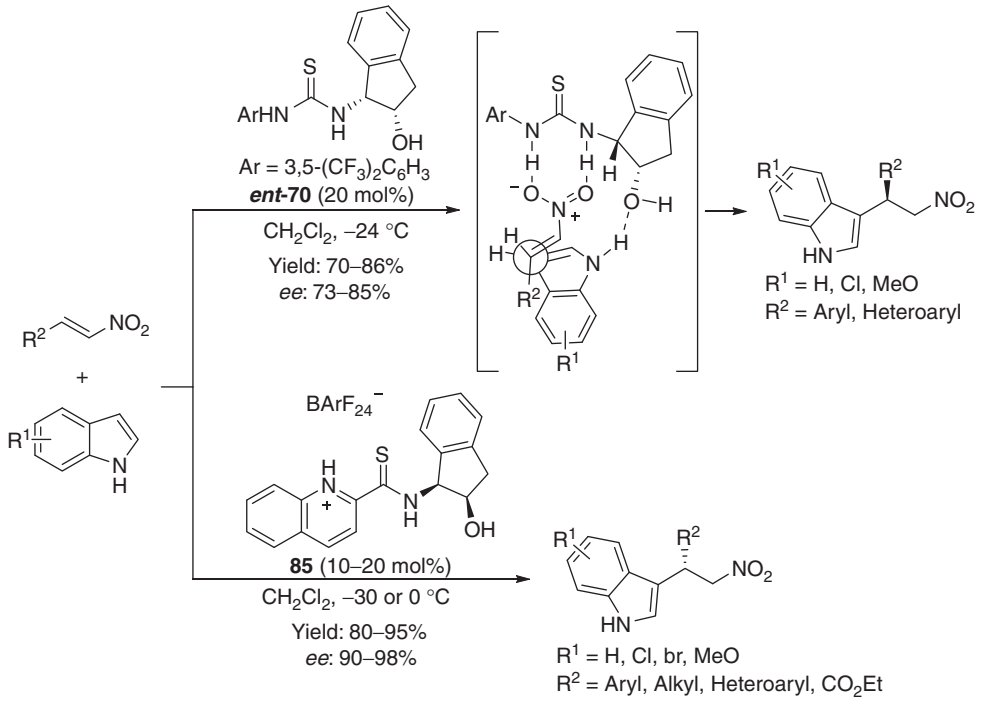


Scheme 60 Enantioselective conjugate Friedel-Crafts alkylations using enones as Michael acceptors.

4.03.3.2 H-Bonding Catalysis

Activating the Michael acceptor through H-bonding interactions is an additional possibility for catalyzing a conjugate Friedel-Crafts alkylation. This, for example, opens the possibility of using nitroalkenes as the electrophilic counterpart in a reaction catalyzed by a chiral thiourea. In this sense, bifunctional thiourea ***ent*-70** has shown up as an excellent promoter for the enantioselective conjugate addition of *N*-unsubstituted indoles to nitroalkenes (Scheme 61).[255] The fact that *N*-methylindole afforded very low levels of enantioselection[256] was an indication of the active participation of the OH group of the catalyst in the reaction, being proposed to engage in a secondary hydrogen-bonding interaction with the indole NH moiety. Interestingly, modification of the thiourea moiety by a quinolinium thioamide led to a much more active and efficient catalyst for the same

reaction (Scheme 61).[257] The better performance of this second catalyst **85** was explained in terms of the presence of a more acidic thioamide H-donor group because of the presence of an additional intramolecular H-bonding interaction between the quinolinium salt and the sulfur atom, which led to a more rigid situation and to a better orientation of the acidic active thiourea site of the catalyst toward the formation of the H-bonding network involved in the activation of the Michael acceptor. Other electron-rich aromatic substrates have also been used with different success as Michael donors in conjugate Friedel-Crafts reactions with nitroalkenes in the presence of bifunctional thiourea catalysts or related structures.[258] Moreover, other Michael acceptors like α,β-unsaturated acyl phosphonates, which are structurally related to nitroalkenes can be employed with good results using this type of catalysts.[259]

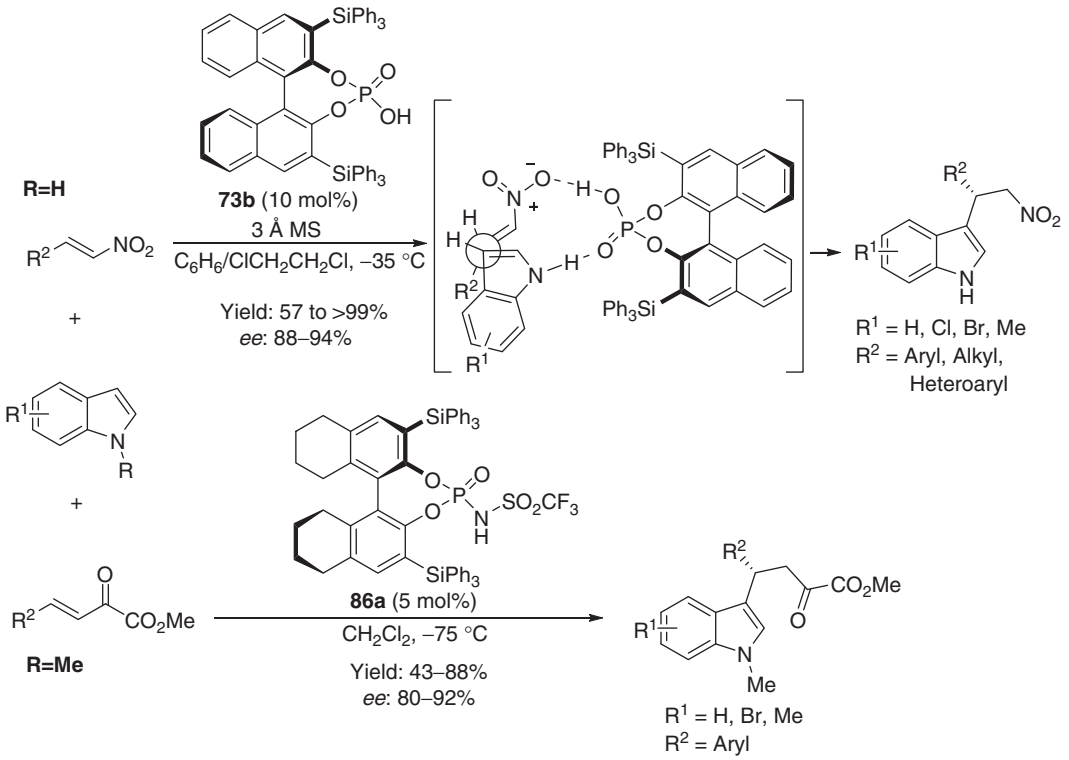


Scheme 61 Enantioselective conjugate addition of indoles to nitroalkenes.

Alternatively, chiral phosphoric acids derived from BINOL have also been identified as effective catalysts for conjugate Friedel-Crafts reactions. These compounds constitute another class of privileged family of organocatalysts that participate in the activation of the Michael acceptor by H-bonding interactions and have been found to be highly efficient in terms of both catalytic activity (because of their higher Brønsted acidity) and stereodirecting ability. For example, the reaction between indoles and a wide variety of nitroalkenes can be carried out in a very efficient way using compound **73b** as the catalyst (Scheme 62).[260] In this reaction, the phosphoric acid plays the role of a bifunctional catalyst in which a double interaction is established between the acidic OH of the catalyst and the nitroalkane on one hand and the acidic NH group of the indole and the P=O moiety on the other. The bulky substituents placed at the 2′-positions of the binaphthyl substructure are required in order to induce stereodifferentiation by steric bias. Other electron-rich systems have also been surveyed with success in this reaction using related BINOL-based chiral phosphoric acids as catalysts.[261] In addition, other possible Michael acceptors that are structurally related to nitroalkenes can be successfully employed as Michael acceptors under this type of organocatalytic activation; in particular, β,γ-unsaturated α-ketoesters as Michael acceptors, which underwent a clean reaction with a variety of indoles using **86a** as the catalyst (Scheme 62).[262] In this case, a more acidic catalyst with an *N*-triflylphosphoramide structure was required for the activation of the substrates and, remarkably, *N*-methyl indoles were found to be very appropriate substrates in the reaction, which indicates that the catalyst is exclusively participating in the activation of the electrophile and, therefore, no secondary interaction with the Michael donor is thought to exist in the transition state.

4.03.4 Stetter Reaction

The ability of *N*-heterocyclic carbenes to activate aldehydes or ketones for their participation as umpoled nucleophiles in the conjugate addition reaction was discovered by Stetter in 1975,[12] when it was found that aldehydes underwent 1,4-addition to electron-deficient olefins in the presence of an *in-situ* generated carbene. This reaction is nowadays referred to as the Stetter



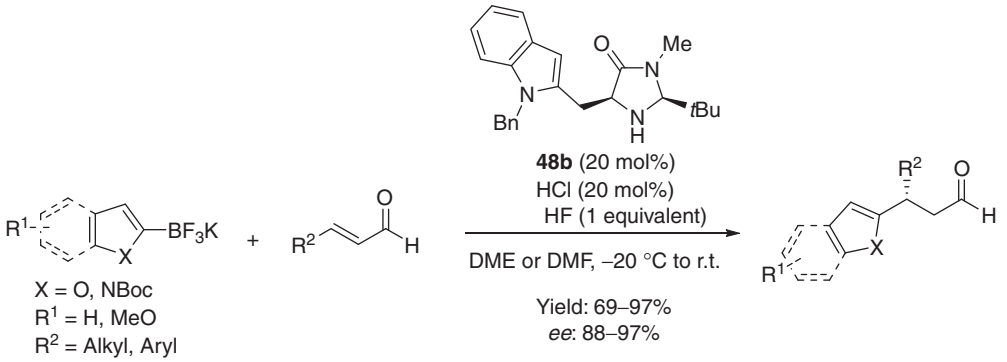
Scheme 62 Phosphoric acids and phosphoramides as catalysts in the enantioselective conjugate Friedel-Crafts alkylation of indoles.

reaction. The overall process leads to the formation of a final adduct with two carbonyl or related groups in 1,4-relative positions, which are not easy to obtain using conventional synthetic methods. Many attempts have been carried out for developing enantioselective variants of this reaction, which in the beginning were mostly limited to intramolecular versions because of the favorable entropic factors generally associated with this type of processes. However, the field has very recently expanded considerably and some very efficient catalytic enantioselective intermolecular Stetter reactions have been reported. As this reaction is the subject of a dedicated full chapter, in this book detailed examples will not be discussed and the reader is directed to the corresponding chapter for further information (*see* Chapter 4.23).

4.03.5 Conjugate Addition of Alkenylboranes and Arylboranes

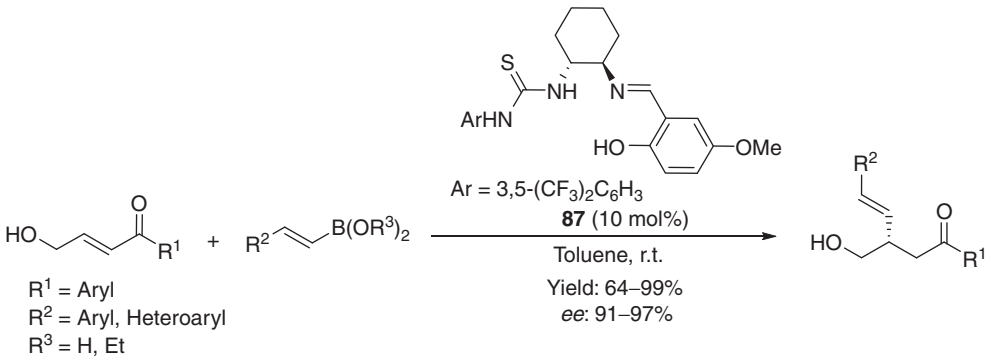
A few organocatalytic enantioselective procedures have appeared in which aryl and vinyl organoboranes can be used as nucleophiles in conjugate addition reactions. The compatibility of these nucleophilic reagents in the presence of water or acidic reagents allows the application of some of the organocatalytic activation mechanisms. For example, the conjugate addition reaction of several differently substituted electron-deficient aryltrifluoroborates to α,β-unsaturated aldehydes can be carried out under iminium activation using the imidazolidinone catalyst **48a** furnishing excellent results with regard to both chemical efficiency and enantioselectivity (Scheme 63).[263] This is a highly valuable and relevant synthetic approach to the functionalization of aromatic and heteroaromatic groups complementary to the Friedel-Crafts reaction, in which the limitation associated with regioselectivity issues and with the requirement of an electron-rich substrate as Michael donor is overcome by using aryl trifluoroborates with any desired substitution pattern as activated π-nucleophiles. The methodology could also be extended to the use of vinylborates as Michael donors with success, remarkably expanding the versatility and synthetic applicability of this methodology.

Hydrogen-bonding catalysis has also been applied to this reaction scheme and, in particular, alkenylboronic acids have been found to be useful nucleophiles in the Michael reactions to enones using chiral thiourea **87** as the catalyst.[264] The reaction required the use of a γ-hydroxylated α,β-unsaturated enone as electrophile, which is proposed to engage in double H-bonding interactions with the boronic acid nucleophile and with the catalyst, directing the reaction in an intramolecular way, with the chiral backbone of the thiourea providing the required steric bias (Scheme 64). There are also some other examples in which chiral diols have been found to catalyze the reaction of a wide variety of alkenylboronates to enones with excellent results.[265] However, the authors usually propose that the activation of the nucleophile should take place by exchange of ligands at boron, leading to a chiral boronate intermediate but with no H-bonding interaction involved during the conjugate addition step.



Scheme 63 Conjugate addition of organotrifluoroborate salts to α,β-unsaturated aldehydes.

Nevertheless, and for similar reasons, the possibility of H-bonding activation mechanism related to that proposed in the previous example cannot be ruled out.



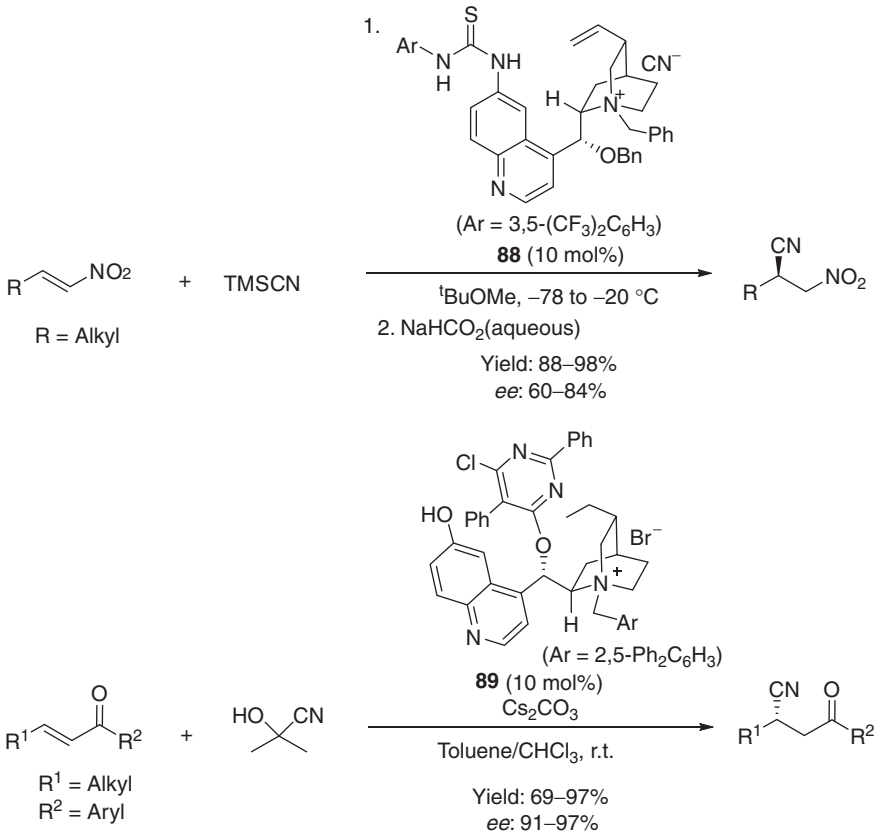
Scheme 64 Enantioselective Michael addition of alkenylboronic acids to γ-hydroxyenones.

4.03.6 Conjugate Addition of Cyanides

The use of cyanide anion as a useful carbon nucleophile in conjugate addition reactions under organocatalytic conditions has only been faced in a couple of successful examples involving different kinds of activation mechanisms (Scheme 65). In a first approach, a bifunctional catalyst **88** was expressly designed for promoting the reaction of trialkylsilyl cyanide to nitroalkenes based on a bifunctional character that combined a tertiary ammonium moiety with a thiourea side chain built on a cinchona alkaloid architecture.[266] The principles behind the catalyst design relied on the ability of the thiourea to engage in H-bonding interactions with the nitroalkene and simultaneously on the capacity of the quaternary ammonium salt to form an ion pair with the cyanide anion, thus leading to a situation in which both the Michael donor and the cyanide nucleophile are activated and placed in close proximity to each other. Another important feature associated with the reaction design is the fact that, once the conjugate addition has taken place, a new molecule of TMSCN exchanges the formed nitronate intermediate with another cyanide anion, releasing the catalyst salt and the conjugate addition product as the corresponding silyl nitronate. For this reason, the reaction had to be quenched with a saturated $NaHCO_3$ solution in order to obtain the desired β-cyano-nitroalkane in good overall yields and in moderate-to-good enantioselectivities. In a second report, cupreidinium salt **89** was used for catalyzing the conjugate addition of cyanide to chalcones and to enoylpyrroles using, in this case, acetone cyanohydrine as the cyanide source.[267] The reaction also involved a bifunctional behavior of the catalyst, with the quaternary ammonium salt engaging in electrostatic interactions with the cyanide anion and the phenolic OH group being involved in H-bonding interactions with the Michael acceptor.

4.03.7 Conjugate Hydrogen Transfer Reaction

The possibility of carrying out enantioselective conjugate reductions under organocatalytic conditions opens up with the introduction of dihydropyridines (also known as Hantzsch esters) as organic compounds that are able to transfer simultaneously a hydride and a proton to the Michael acceptor.[268] This consists of a biomimetic approach in which the dihydropyridine reagent



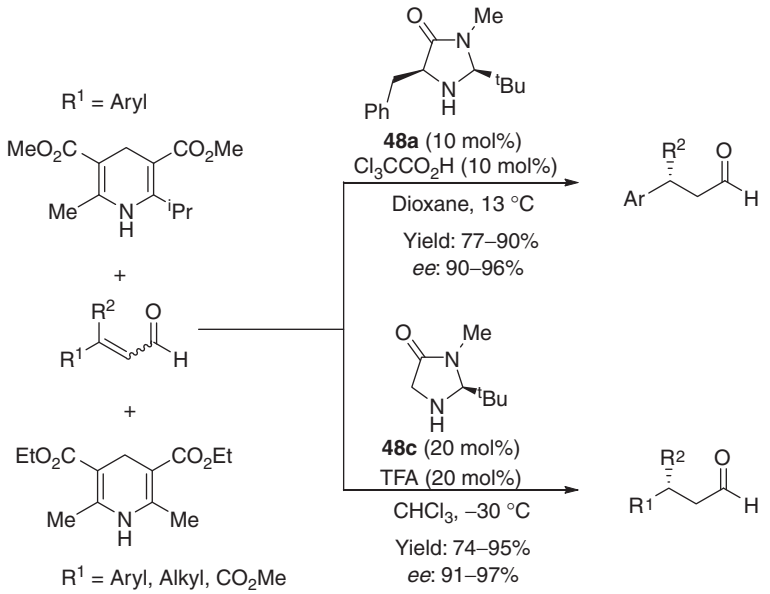
Scheme 65 Organocatalytic enantioselective conjugate addition reactions employing cyanides as Michael donors.

mimics the behavior of the standard reduction cofactors like NADH or $FADH_2$ employed by Nature in biological processes. In this sense, both iminium activation and H-bonding catalysis have been employed with great success in many examples of conjugate reduction of electron-poor olefins.

4.03.7.1 Iminium Catalysis

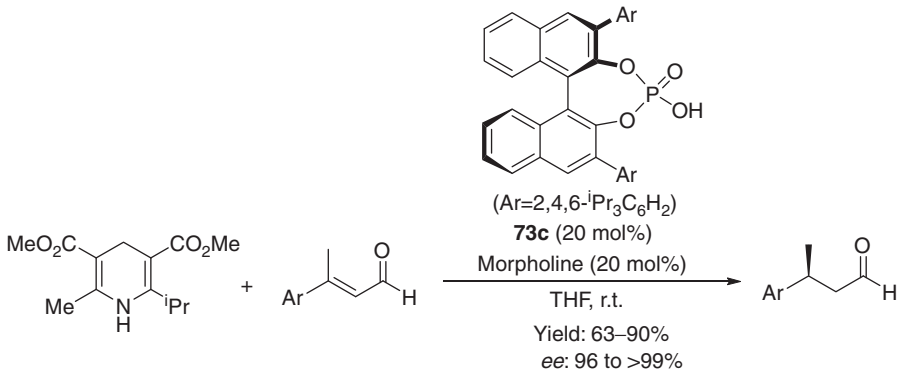
Imidazolidinone **48a** catalyzes the reduction of β-substituted α,β-unsaturated aldehydes in the presence of a bulky Hantzsch ester as the hydride-donor reagent (Scheme 66).[269] The reaction proceeded with very high efficiency, providing excellent yields and enantioselectivities for all the substrates, although in all cases incorporating an aromatic substituent at the β-position. Interestingly, the double-bond geometry of the Michael acceptor did not show to have any influence in the stereochemical outcome of the reaction, observing that enals of different configurations furnished the same enantiomer after reduction, which was interpreted in terms of a rapid Z/E isomerization of the starting materials catalyzed by the imidazolidinone catalyst during the formation of the intermediate iminium ion. A similar reduction protocol was simultaneously and independently reported,[270] showing that less bulky imidazolidinone **48c** containing a single stereogenic center could also play the role of an outstanding catalyst for this transformation (Scheme 66) with a wide substrate scope that allowed the use of enals containing both aliphatic and aromatic substituents at the β-position. This catalyst was also able to reduce the Michael acceptors containing bulky substituents. This reaction was also diastereoconvergent, observing that both Z or E α,β-unsaturated aldehydes furnished the same enantiomer after the reduction, which also allowed the use of Z/E mixtures of the starting Michael acceptors without erosion on the enantioselectivity. Cyclic enones can also be reduced in a very efficient way using a related imidazolidinone catalyst.[271]

Working in this reaction, a new concept for organocatalytic activation was developed, which relies on the close association that occurs between the ion pairs in polar reactions proceeding via charged intermediates when conducted in nonpolar organic solvents. This implies that the counteranion associated with the intermediate iminium cation could remain near the position in which the conjugate addition takes place, which can lead to the possibility of stereocontrol by introducing chiral elements on this counterion. This approach known as the Asymmetric Counterion-Directed Catalysis (ACDC) was applied to the conjugate reduction of enals using Hantzsch esters as hydride donors observing that chiral phosphoric acid **73c** (TRIP) together with morpholine were able to catalyze this reaction in a very efficient way (Scheme 67).[272] This concept has also been applied to the enantioselective transfer hydrogenation of enones but, in this case, a primary amine had to be employed as the iminium-forming



Scheme 66 Enantioselective transfer hydrogenation of α,β-unsaturated aldehydes.

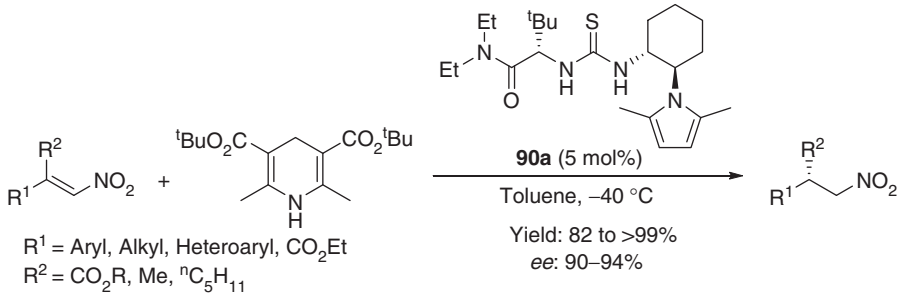
reagent as a more active amine catalyst with improved abilities to condense with the enone for the formation of the activated iminium ion.[273]



Scheme 67 The ACDC concept in the enantioselective transfer hydrogenation α,β-unsaturated aldehydes.

4.03.7.2 H-Bonding Catalysis

Thioureas have also been found to catalyze the conjugate reduction of nitroalkenes also using Hantzsch esters as the reducing agents. For example, Jacobsen thiourea **90a** has shown to perform excellently in the enantioselective conjugate reduction of β,β-disubstituted nitroalkenes furnishing the corresponding adducts incorporating a β-stereogenic center in good yields and enantioselectivities (Scheme 68).[274] The reaction behaved very well when one of the β-substituents was either an aromatic or a



Scheme 68 Enantioselective conjugate reduction of β,β-disubstituted nitroalkenes catalyzed by **90a**.

heteroaromatic moiety or, alternatively, when the differences in bulkiness between the two substituents was rather big. The methodology was also applied to the conjugate hydrogen transfer of β-nitroacrylates, which results in a direct approach to α-substituted β-amino acids after convenient reduction of the nitro group. Importantly, in this case the stereochemical outcome of the reaction was found to be strongly dependent on the double-bond geometry observing that *E* or *Z* nitroolefins furnished opposite enantiomers, which therefore required the use of highly diastereopure starting materials for attaining good enantioselectivities.

4.03.8 Conjugate Addition of Heteronucleophiles

The search for procedures for carrying out the enantioselective conjugate addition of heteroatom-centered nucleophiles to electron-deficient olefins (also known as hetero-Michael reaction) using organocatalysis as the methodological approach has also been intense. In this context, many different examples can be found in the recent literature regarding the use of different types of nucleophiles such as sulfur-,[275] oxygen-,[276] nitrogen-,[277] phosphorous-,[278] boron-, or silicon[279]-based Michael donors. In general, the main difficulties associated with the use of this type of heteronucleophiles in this particular transformation is related to the reversibility of the conjugate addition process, which very often leads to low conversions or low configurational stability of the final compounds in many cases. For this reason, special strategies for overcoming this problem had to be devised, which typically involve a careful design of the Michael donor reagent or, alternatively incorporating an additional electrophile to the reaction design in order to quench the hetero-Michael addition product in a typical cascade process either intra- or intermolecularly. All these cascade reactions are not covered herein.

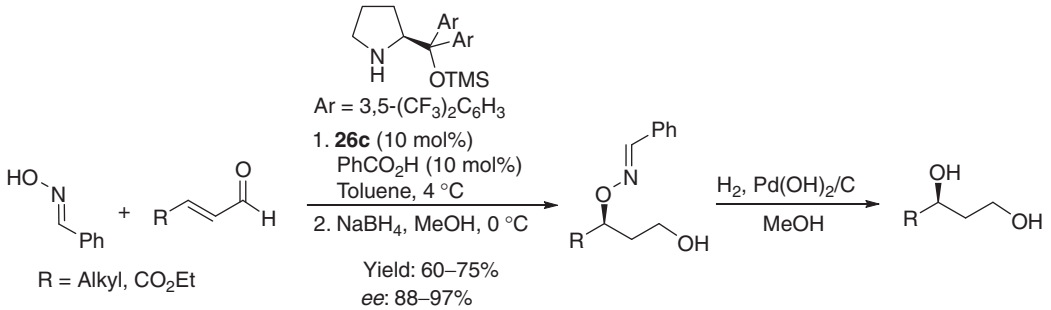
4.03.8.1 Iminium Catalysis

The iminium activation concept has proved to be very useful for catalyzing the conjugate addition of heteroatom-centered nucleophiles to α,β-unsaturated aldehydes and enones. As it has been shown in all preceding cases, the typical situation involves the use of secondary amines when working with enals as the Michael acceptors, whereas primary amines are more active and efficient catalysts when enones are used. In addition, this particular activation approach is very appropriate for the development of cascade processes because of the intrinsic mechanistic profile of the process, in which a stable enamine is generated after the conjugate addition step that can participate as the reactive nucleophilic species in a subsequent reaction with an electrophile. However, as pointed out before, these particular cases are not covered herein.

4.03.8.1.1 Oxa-Michael reaction

The conjugate addition of oxygen-centered nucleophiles to α,β-unsaturated aldehydes or ketones under iminium activation is one of the most challenging reactions among all organocatalytic Michael-type reactions. In addition to the already mentioned low configurational stability of the oxa-Michael adducts associated with the highly reversible character of the reaction, the low nucleophilicity exhibited by the most common oxygen nucleophiles like water, alcohols, or carboxylates and their tendency to undergo 1,2-addition rather than the desired conjugate addition process makes this transformation specially difficult.

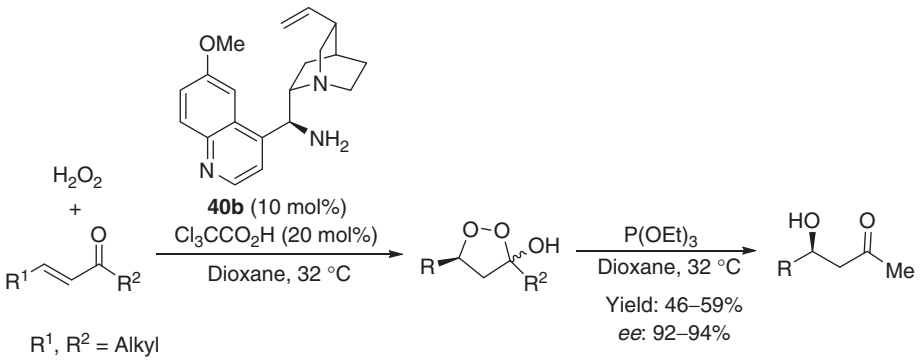
The reaction using aliphatic alcohols as nucleophiles in the enantioselective conjugate addition to enals has been studied, but with limited success with regard to enantiocontrol.[280] An efficient alternative to solve the low reactivity associated with the oxygen-centered nucleophile has involved the use of aromatic oximes as the convenient Michael donors, which were found to be active Michael donors in the reaction with enals under *O*-TMS diarylprolinol **26c** catalysis (Scheme 69).[281] This is a remarkably fast reaction but the tendency to racemization shown by the conjugate addition products required careful monitoring of the process and *in-situ* reduction to the stable corresponding primary alcohols after observing full conversion. The reaction was remarkably broad in scope for β-alkyl-substituted enals but failed in the case of β-aryl substituted substrates. An important advantage of the methodology was found on the easy cleavage of the O–N bond, which resulted in a very simple procedure for the



Scheme 69 Organocatalytic enantioselective conjugate addition of oximes to enals.

asymmetric synthesis of 1,3-diols. The same kind of nucleophiles were employed afterwards in the reaction using enones as the Michael acceptors,[282] in this case using a primary amine derived from using hydroquinine as the catalyst.

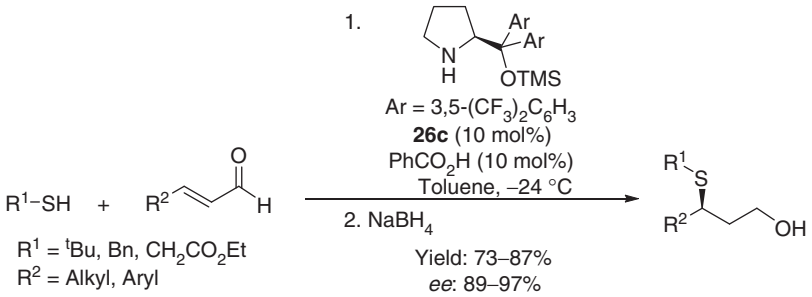
Hydrogen peroxide has also been employed as a nucleophile in this context with different results. In this sense, while the reaction using aldehydes as Michael donors usually furnishes the corresponding α,β-epoxy aldehydes through cascade oxa-Michael/cyclization process,[283] the incorporation of enones as electrophiles to the reaction scheme stops at the initial oxa-Michael addition step because the β-hydroperoxide intermediate undergoes fast intramolecular reaction with the carbonyl group, furnishing a stable 1,2-dioxolan-3-ol derivative as the final reaction product.[284] The formation of this cyclic derivative operates as the driving force for the reaction, avoiding the retroaddition process and accounts for the high conversion observed. In this context, the primary amine **40b**-catalyzed reaction of several enones with H_2O_2 proceeded with moderate yields but with excellent enantioselectivities, and the 1,2-dioxolane adducts could be easily transformed into β-hydroxy ketones by reduction (Scheme 70). The same reaction using alkyl hydroperoxides as oxygen-centered nucleophiles has also been carried out using the same catalyst and showing a similar behavior, although in this case the nature of the alkyl hydroperoxide nucleophile had to be carefully selected in order to obtain preferential β-peroxidation versus the corresponding epoxide.[285]



Scheme 70 Enantioselective hydroperoxydation of enones catalyzed by **40b.**

4.03.8.1.2 Sulfa-Michael reaction

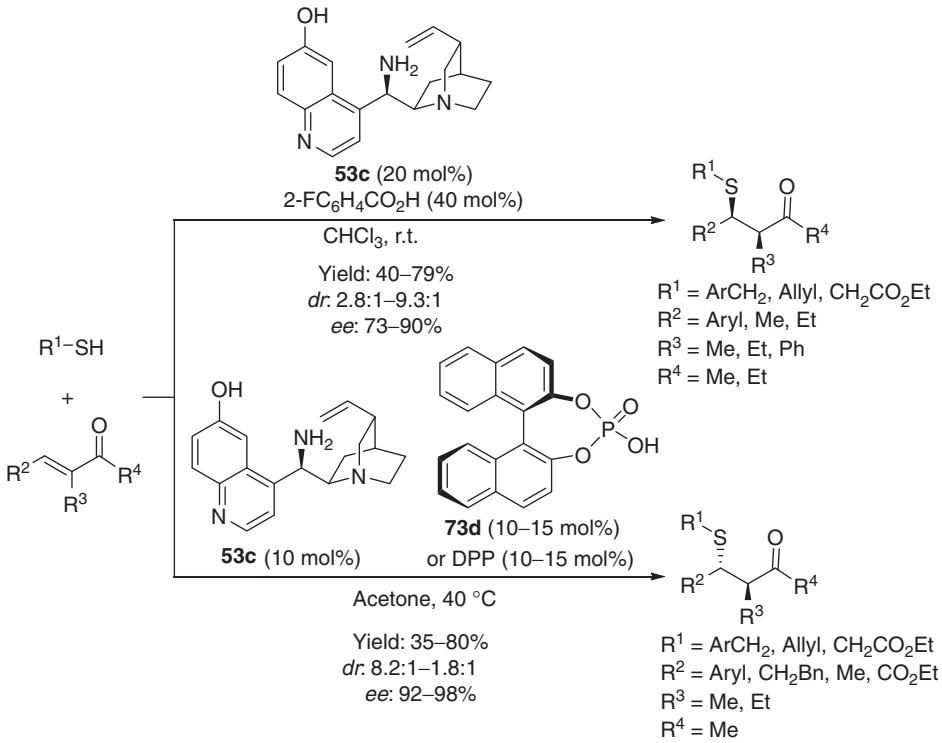
O-TMS protected diarylprolinol **26c** also catalyzes the conjugate addition of thiols to α,β-unsaturated aldehydes in a very efficient manner (Scheme 71). As it happened with the parent oxa-Michael reaction using oximes as pronucleophiles, the low configurational stability of the adducts at room temperature implied that the reaction had to be carried out at a low temperature and also that the conjugate addition products had to be reduced *in situ*, furnishing the corresponding γ-thio alcohols in excellent yields and enantioselectivities.[286] Both β-alkyl- and β-aryl-substituted enals could be used as suitable Michael acceptors in this reaction and, furthermore, different thiols like *tert*-butyl mercaptan, benzyl mercaptan, or even functionalized thiols were evaluated resulting in all cases equally effective nucleophiles to be used in this reaction.



Scheme 71 Enantioselective sulfa-Michael reaction of thiols with α,β-unsaturated aldehydes.

The same reaction involving α,β-unsaturated ketones as Michael acceptors has also been reported using a chiral primary amine catalyst.[287] In this sense, a very interesting study has been reported detailing the use of α-branched enones as Michael acceptors in the sulfa-Michael reaction with alkylthiols employing quinidine-based catalyst **53c** and showing the possibility of obtaining any desired *syn* or *anti* configured product by simply changing the nature of the acid cocatalyst incorporated (Scheme 72).[288] In this sense, although the reaction in the presence of 2-fluorobenzoic acid proceeded smoothly to deliver the 1,3-*syn* adduct, changing to diphenylphosphoric acid led to the preferential formation of the corresponding 1,3-*anti* diastereoisomer, in all cases with an excellent level of enantiocontrol. The latter situation could be further optimized in terms of higher diastereoselectivity using a chiral phosphoric acid such as **73d**. As it can be seen from Scheme 72, both the conditions led to the formation of the

sulfa-Michael adduct with the same configuration at the α-stereocenter the origin of the formation of two diastereoisomers on the different sense of enantioinduction being exerted by the catalyst during the conjugate addition step. The researchers explain this behavior in terms of the conformational flexibility of the chiral primary amine catalyst scaffold which, on protonation with the Bronsted acid cocatalyst forms an ion-paired assembly that adopts different spatial arrangements depending on the nature of the Bronsted acid employed and the strength of the ion-cation interaction. In fact, when even bulkier phosphoric acids (which bind more weakly to the catalyst because of steric constraints) were employed, the reaction was found to be *syn* selective again.



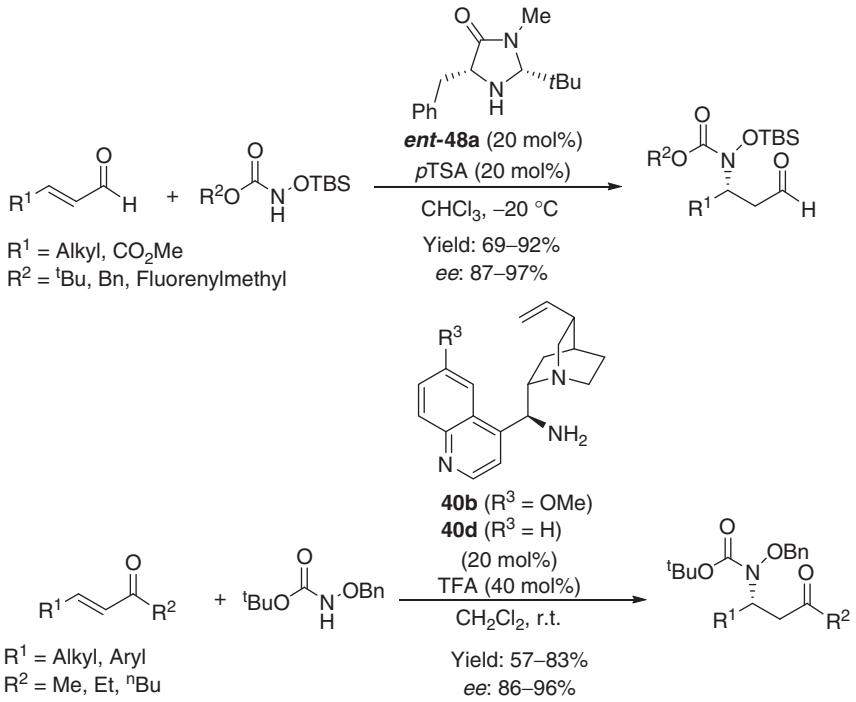
Scheme 72 Enantioselective sulfa-Michael reaction of thiols with α-branched enones.

4.03.8.1.3 Aza-Michael reaction

The conjugate addition of nitrogen nucleophiles to carbonyl compounds represents a very attractive procedure for the asymmetric synthesis of β-amino carbonyl compounds, and, for this reason, the development of enantioselective organocatalytic methods has also been the focus of intensive research, especially in the past few years. However, the aza-Michael reaction using the iminium activation concept represents a very challenging situation, mainly because of the additional chemoselectivity issues associated with the fact that both the catalyst and the nucleophile are amine species, which implies that the role of both the reagents must be clearly controlled. This means that the chiral amine catalyst must not undergo conjugate addition reaction (which would eventually lead to catalyst consumption) and, on the other hand, the amine reagent selected as the nucleophile must not participate in the iminium ion formation (which would lead to the formation of a racemic product). In addition, reversibility of the reaction is also an additional problem that may lead to low conversions and/or poor enantioselectivities.

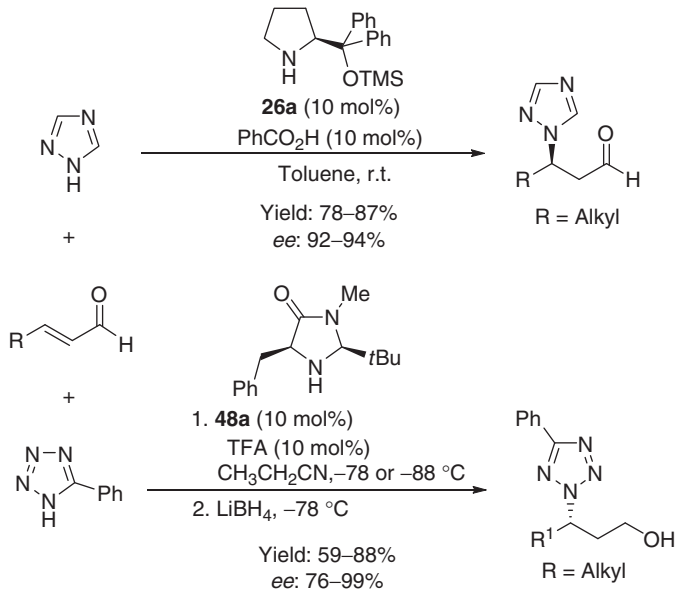
In this context, several very successful examples of aza-Michael reaction under iminium activation have been developed in which these chemoselectivity issues have been usually addressed by careful design of the Michael donor. For example, *N*-*tert*-butyldimethylsilyloxycarbamates show up as a very efficient pronucleophile for the reaction with α,β-unsaturated aldehydes in the presence of chiral imidazolidinone ***ent*-48a** catalyst (Scheme 73).[289] These silyloxycarbamates show an enhanced nucleophilicity due to the so-called α-effect, exerted by the presence of the trialkylsilyloxy moiety directly attached to the nitrogen atom. In addition, the introduction of the carbamate functionality results in the formation of a nonbasic *N*-protected β-amino carbonyl compound as the reaction product, thus avoiding the reversibility of the reaction. The closely related *N*-methoxycarbamates[290] and *N*-hydroxy carbamates[291] can also be employed as nucleophiles in the same reaction, in this case using *O*-trimethylsilyldiphenylprolinol as the catalyst. The addition of *N*-benzyloxy carbamates to enones has also been carried out with the help of bifunctional catalysts **40b** and **40d** containing a primary amine moiety together with the additional quinuclidine basic site able to interact with the *N*-nucleophile (Scheme 73).[292]

Aromatic nitrogen heterocycles containing acidic NH groups have also been employed as suitable *N*-nucleophiles in this reaction. For example, 1,2,4-triazole and other related triazoles add smoothly to α,β-unsaturated aldehydes in the presence of **26a**



Scheme 73 Enantioselective aza-Michael reactions using silyloxycarbamates and alkoxycarbamates as Michael donors.

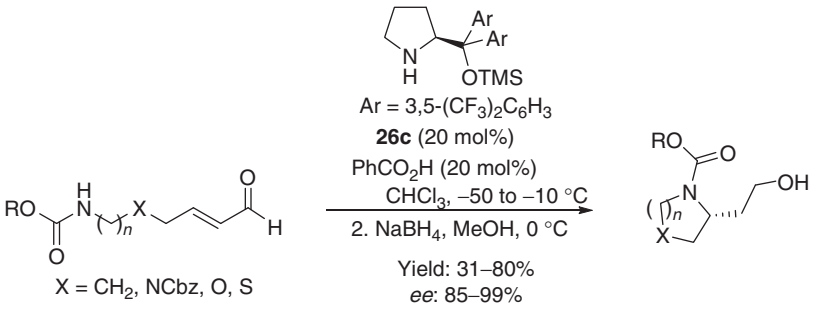
as the catalyst furnishing the final adducts with a remarkable degree of stereocontrol.[293] The best results were obtained using 1*H*-1,2,4-triazole as the nucleophile, because it led to the formation of configurationally stable compounds in very good yields and enantioselectivities. In an attempt to broaden the scope of the reaction other heterocycles were tested as nucleophiles such as 5-phenyl-1*H*-tetrazole, 2*H*-1,2,3-triazole, and 1*H*-benzo[*d*][1,2,3]triazole but in these cases the adducts had to be reduced *in situ* in order to avoid racemization. Alternatively, the conjugate addition of 5-phenyl-1*H*-tetrazole to α,β-unsaturated aldehydes can also be carried out using imidazolidinone **48a** as the catalyst (Scheme 74).[294] In the same way as it happened for the reaction catalyzed by diarylprolinol derivative **26a**, the low configurational stability of the aza-Michael adducts required to carrying out a third *in-situ* reduction and also the reaction had to be carried out at very low temperatures which resulted in very long reaction times in order to achieve synthetically useful yields. Other nitrogen heterocycles like pyrazoles, pyrroles, or succinimides have also been surveyed in the reaction with enals, in these cases again involving the use of diarylprolinol derivatives as the most efficient



Scheme 74 Nitrogen heterocycles as Michael donors in organocatalytic aza-Michael reactions.

catalysts.[295] On the other hand, the conjugate addition of benzotriazol, 9-phenyltetrazol, and 2-pyrazolin-5-ones to enones under primary amine catalysis has also been reported with success.[296]

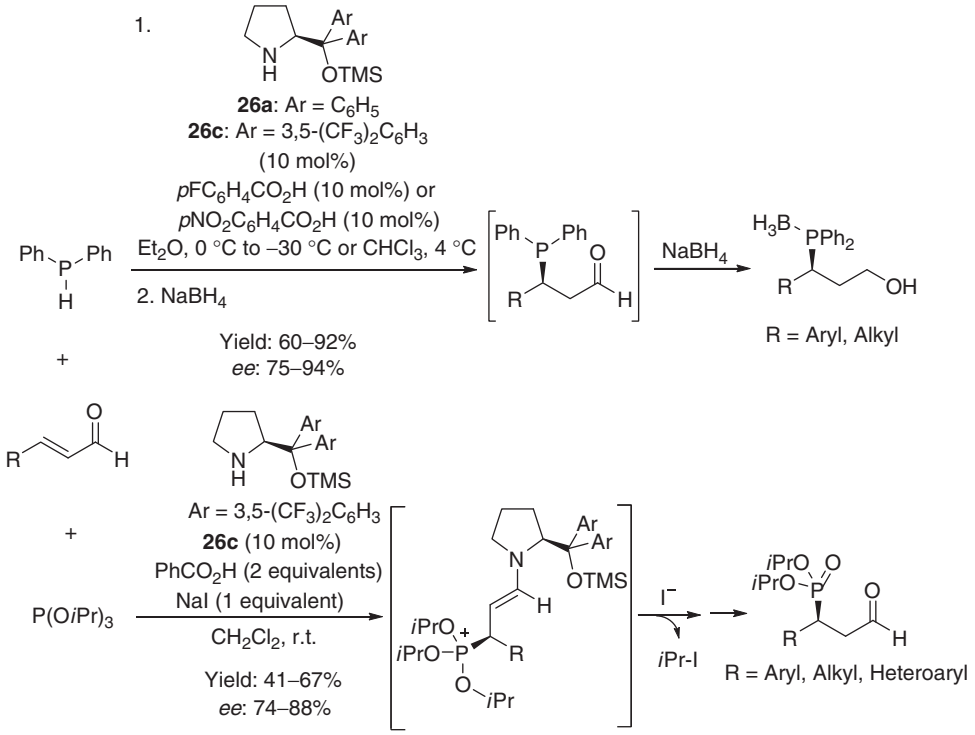
The aza-Michael reaction carried out in an intramolecular fashion can also be a very useful and direct approach to the preparation of nitrogen heterocycles. The reaction design includes an α,β-unsaturated aldehyde containing a functionalized side chain at the β-position, which contains the nitrogen-based pronucleophile. As it happened in the previous examples, the reversibility of the reaction resulted in low configurational stability of the obtained adducts and therefore reduction of the formyl group had to be carried out *in situ* for the isolation of the final compounds. Catalyst **31c** was employed as the most effective promoter of the reaction using substrates with tethers of different lengths between the enal and the amino moieties, and also evaluating the incorporation of intercalating heteroatoms for the preparation of different heterocyclic structures (Scheme 75).[297]



Scheme 75 Organocatalytic intramolecular aza-Michael reactions.

4.03.8.1.4 Phospha-Michael reaction

The phospha-Michael reaction was one of the latest hetero-Michael reactions to be developed under iminium activation, mainly because of the difficulties associated with the identification of a suitable phosphorous-based pronucleophile due to the high tendency of phosphines to undergo oxidation in the presence of air. The conjugate addition of the relatively easier to handle diphenylphosphine to α,β-unsatuarted aldehydes can be carried out with good yields and enantioselectivities in the presence of an *O*-trimethylsilyl diarylprolinol like **26a** or **26c** as catalysts and also incorporating a benzoic acid cocatalyst (Scheme 76).[298] The phospha-Michael adducts had to be reduced *in situ* and the phosphine moiety had to be protected as the corresponding



Scheme 76 Organocatalytic enantioselective phospha-Michael reactions.

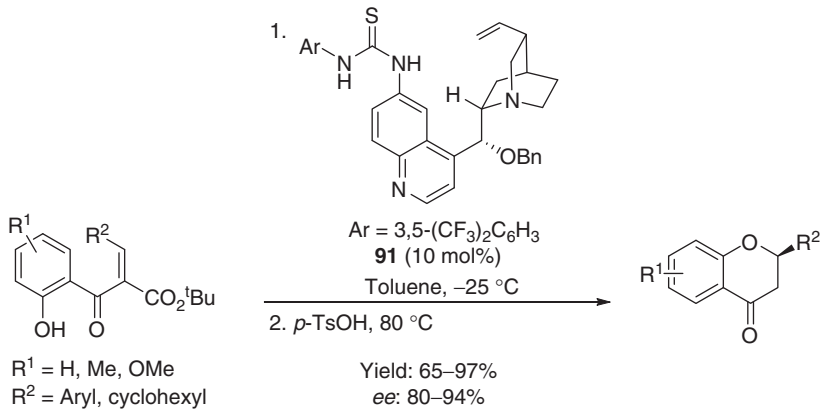
phosphine–borane complex for better isolation and purification. The nature of the Brønsted acid cocatalyst was also decisive for achieving good stereocontrol, with the slightly more acidic *p*-nitrobenzoic acid and *p*-fluorobenzoic acid as the additives that furnished the best enantioselectivities. However, phosphites have also been employed as suitable and very convenient phosphorous pronucleophiles, also in the reaction with enals and once again involving the use of the privileged *O*-TMS diarylprolinol catalyst **26c**.[299] In this case, NaI was incorporated as a stoichiometric additive, which initiated an intermolecular nucleophilic substitution process on the initially formed phospha-Michael adduct, leading to the formation of a final phosphonate moiety. There is also one single example of a phospha-Michael reaction using enones as Michael acceptors, which involves the use of diphenylphosphine oxide as the phosphorous pronucleophile and a bifunctional primary amine/thiourea catalyst.[300]

4.03.8.2 H-bonding Catalysis

The ability of chiral Brønsted acids to activate the Michael acceptor through H-bonding interactions has also been applied as a very effective tool for developing catalytic asymmetric methodologies that allow to carry out hetero-Michael reactions with high yields and enantioselectivities. As it happened in the related standard Michael reaction, the thiourea moiety constitutes a privileged structure for engaging the formation of H-bonded networks with the electron-withdrawing group of the Michael acceptor which, in addition, typically incorporate a second Brønsted base functionality for the activation of the heteronucleophile.

4.03.8.2.1 Oxa-Michael reaction

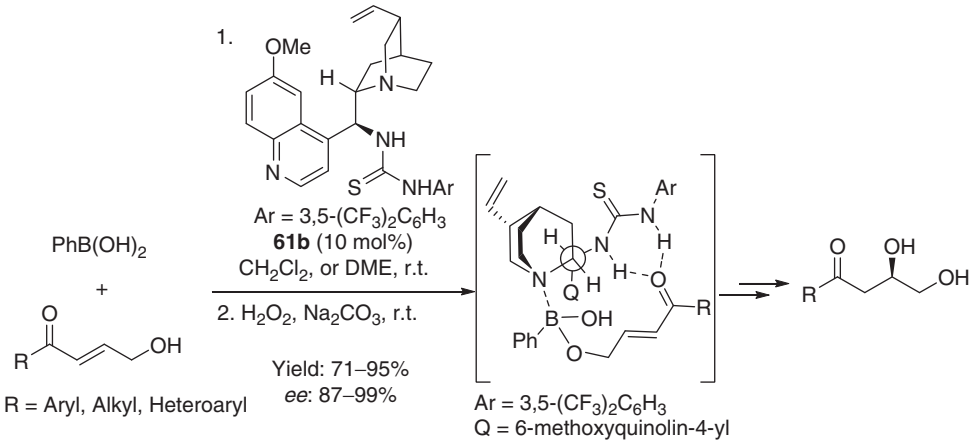
A few examples of oxa-Michael reactions proceeding via H-bonding activation have been reported up to date in the literature, most of them being intramolecular reactions and also involve acidic alcohols like phenols as oxygen-based Michael donors. A good example is shown in Scheme 77, in which bifunctional cinchona-thiourea catalyst **91** was developed to promote the intramolecular oxa-Michael reaction of an *ortho*-substituted phenol containing a functionalized side chain incorporating a doubly activated olefin,[301] leading to the formation of the chromane skeleton. The reaction proceeded with excellent yields and enantioselectivities. A subsequent acid-mediated decarboxylation step, which was carried out in a one-pot manner, furnished the corresponding flavanones in a single step with excellent yields and enantioselectivities. The presence of this highly electron-deficient olefin as the Michael acceptor was found to be crucial for the success of the reaction, because its high reactivity allowed to carry out the reaction at lower temperatures without affecting conversion and this also resulted in improved enantioselectivity.



Scheme 77 Organocatalytic intramolecular oxa-Michael reaction under H-bonding catalysis.

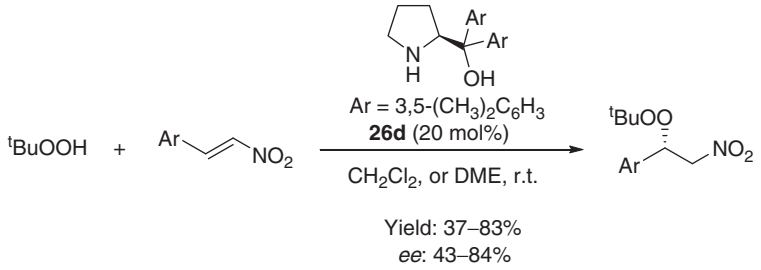
There is also an interesting example of an enantioselective thiourea-catalyzed oxa-Michael reaction using γ-hydroxy α,β-unsaturated ketones as Michael acceptors in which a phenylboronic acid was employed as the hydroxyl anion equivalent (Scheme 78).[302] The reaction proceeded in an intramolecular way, starting with the reaction of the boronic acid with the γ-hydroxy group of the functionalized Michael acceptor forming a boronate intermediate, which subsequently becomes an effective reagent for the intramolecular transfer of the remaining OH group. The reaction proceeded in a highly enantioselective way incorporating thiourea **61b** as catalyst and providing a series of β,γ-dihydroxy ketones in excellent yields after an oxidative work-up. The bifunctional nature of the tertiary amine-thiourea catalyst implies that the boronate intermediate also was activated by interacting with the basic quinuclidine nucleus and the thiourea moiety engaged in double H-bonding interactions with the enone carbonyl group. δ-Hydroxy enones were also found to be suitable substrates required to carry out the reaction at higher temperatures but still furnishing excellent results, although bulkier and more electron-rich arylboronic acids were required in some cases.

Finally, diarylprolinol **26d** has also been employed as catalyst in the enantioselective β-peroxydation of nitroalkenes with *tert*-butyl hydroperoxide (Scheme 79).[303] In this particular case, the catalyst is proposed to engage in a bifunctional activation mode, which on one hand assists the deprotonation of the hydroperoxide and on the other activates the nitroalkene by the formation of



Scheme 78 Enantioselective oxa-Michael reaction of phenylboronic acid with γ-hydroxyenones.

one H-bond with the nitro group. Under optimized conditions, moderate yields and enantioselectivities of approximately 85% *ee*, were achieved for a variety or nitrostyrene derivatives.



Scheme 79 Enantioselective β-peroxidation of nitroalkenes using aminoalcohol **26d** as the catalyst.

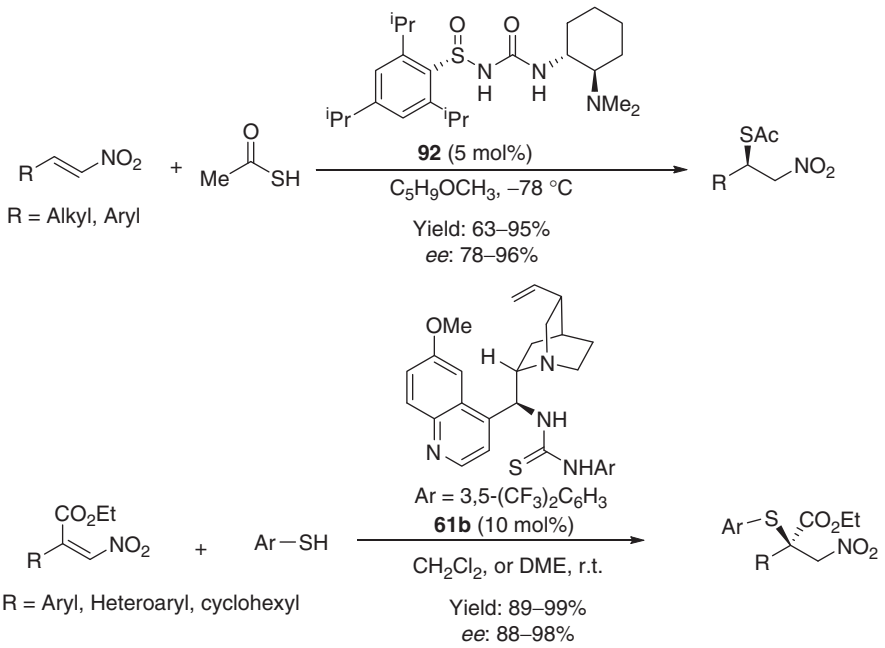
4.03.8.2.2 Sulfa-Michael reaction

The combined use of nitroalkenes as Michael acceptors and chiral thiourea as catalyst has been extensively exploited in this reaction, which again shows that the most effective catalysts are those with a bifunctional nature in which an additional Brønsted basic site is incorporated. In this context, *N*-sulfinylurea **92** has been identified as an excellent catalyst for the conjugate addition of thioacetic acid to nitroalkenes, furnishing the corresponding adducts in good yields and enantioselectivities under optimized conditions (Scheme 80).[304] Alternatively, the sulfa-Michael reaction between arylthiols and α-substituted β-nitroacrylates has been described using cinchona-thiourea **61b** as the catalyst accessing to products with a sulphur-containing quaternary stereocenter, which can also be further manipulated at the nitro group.[305] This reaction was found to occur in a fully regioselective way, with the nitro group showing up as the dominant element for the activation of olefin as a Michael acceptor.

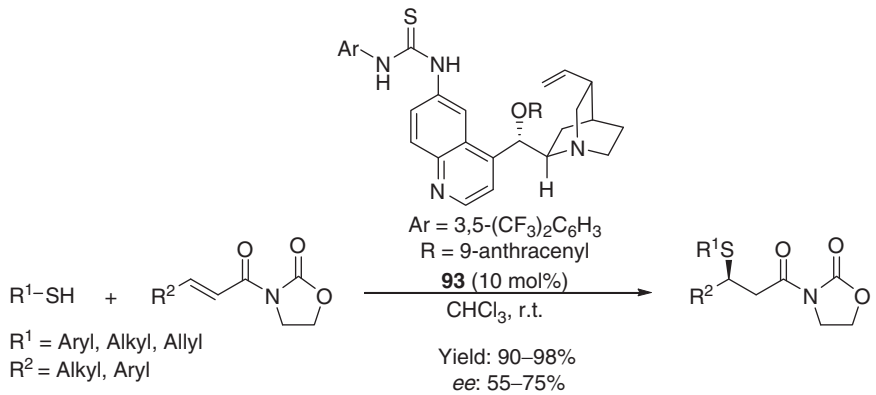
The structural and electronic analogies between the nitro and other functional groups have also been employed to expand the scope of this transformation to other Michael acceptors. This is the case of the α,β-unsaturated imides, which undergo a smooth reaction with alkyl and arylthiols in the presence of this type of bifunctional thiourea catalysts. In the case shown in Scheme 81, quinidine-thiourea catalyst **93** has demonstrated an excellent performance in the conjugate addition of alkyl thiols to *N*-enoyl oxazolidinones, obtaining outstanding results for a variety of both Michael donors and acceptors tested.[306] Other related substrates able to engage H-bonding interaction events with thioureas or squaramides like α,β-unsaturated sulfonates[307] or crotonates[308] have also been tested with success. This also includes the use of enones, a reaction that is limited to chalcones, which were known to undergo reaction with thiophenol or thioacetic acid in the presence of cinchona alkaloid-based catalysts furnishing the expected conjugate addition products since the very early studies carried out by Wynberg in 1981.[309]

4.03.8.2.3 Aza-Michael reaction

α,β-Unsaturated amides derived from 3,5-dimethyl-1H-pyrazole have been explored as suitable Michael acceptors able to engage in multiple H-bonding interactions with a chiral thiourea catalyst in one very efficient example of aza-Michael reaction using hydroxylamines as the *N*-nucleophiles (Scheme 82).[310] In fact, computational studies demonstrated that the thiourea moiety was involved in a double H-bond formation with the *N*-2 of the pyrazole unit and that the remaining OH group would be responsible for the activation of the carbonyl group and also for the transference of the N-nucleophile via an additional H-bonding interaction. Moreover, this study demonstrated that the conformation of the pyrazole amide group was crucial for achieving a high



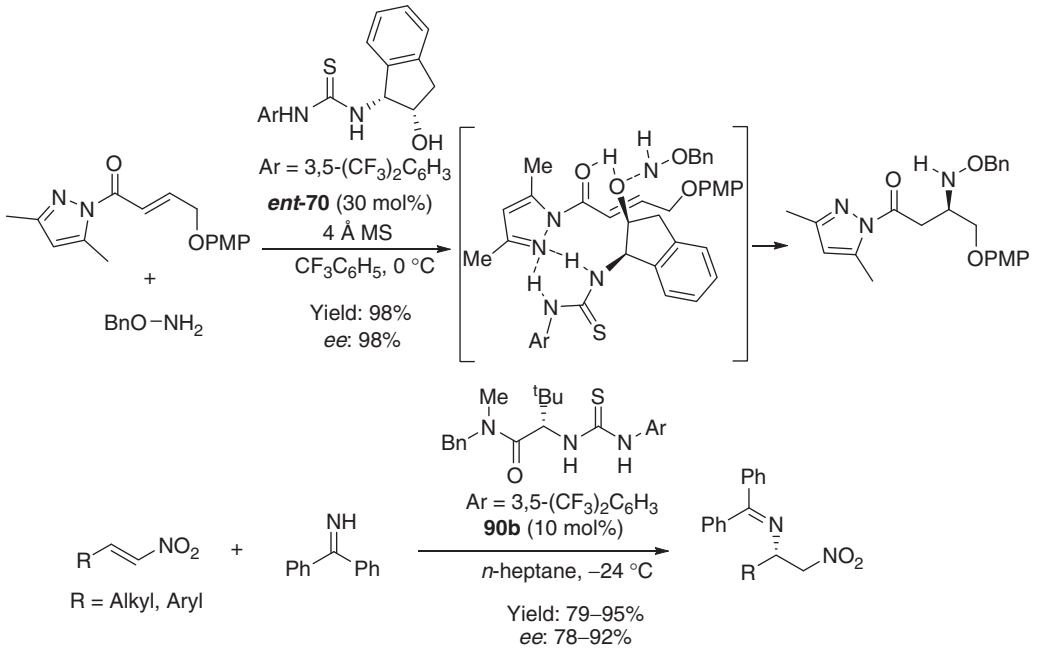
Scheme 80 Ureas and thioureas as catalysts in enantioselective sulfa-Michael reactions using nitroalkenes as Michael acceptors.



Scheme 81 Enantioselective sulfa-Michael reaction of aryl and alkylthiols with α,β-unsaturated imides.

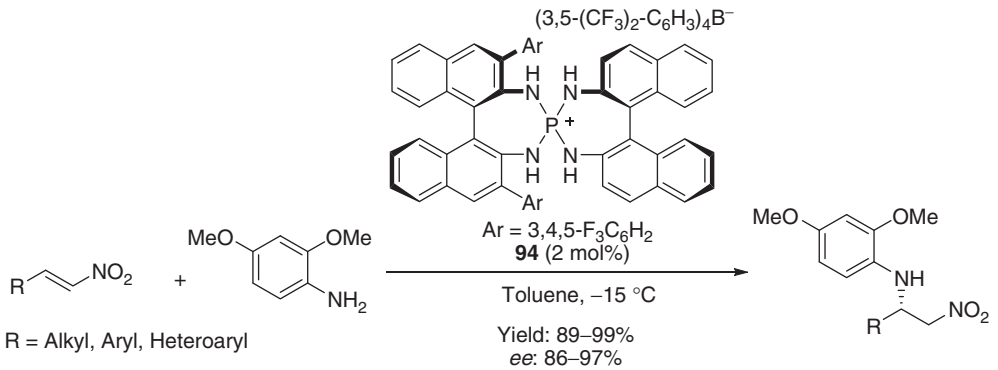
stereocontrol, showing that the reaction should proceed via an intermediate in which the O=C-N-N substructure would remain in a preferred *s-trans* conformation, which favored over the corresponding *s-cis* geometry, the latter furnishing the minor enantiomer. It has to be pointed out that in almost all cases the thiourea ***ent*-70** was employed in stoichiometric amounts, although there is one example showing the possibility of using a 30 mol% of thiourea additive to promote the reaction, providing an excellent yield and enantioselectivity of the aza-Michael adduct. In a different approach, nitroalkenes have been used as the Michael acceptor in the presence of a chiral thiourea catalyst like **90b** for carrying out the aza-Michael reaction employing benzophenone imine as the Michael donor.[311] The easy hydrolysis of the imine moiety present at the conjugate addition product shows that this particular *N*-unsubstituted imines are excellent ammonia equivalents to be used in this type of reactions.

There is also one example of an aza-Michael reaction using nitroalkenes as the Michael acceptor, which involves the use of anilines as Michael donors and where a chiral arylaminophosphonium salt has been used as a chiral Brønsted acid catalyst (Scheme 83).[312] A short study was carried out directed toward the optimization of the catalyst structure, which included modification in the substitution pattern of the 3 and 3′ positions of the binaphthyl backbone and the use of the combination of the (*R*,*R*) and the (*R*,*S*) binaphthyl moieties. The authors also investigated the nature of the aniline derivative used as the Michael donor, observing that the *ortho*-substituted anilines were the most efficient for the aza-Michael reaction. An important feature associated with this methodology is the possibility to modify the arylamino group introduced with the Michael donor for the conversion of the obtained adducts into the corresponding *N*-Boc-protected amines. On the contrary, some examples also exist regarding the conjugate addition of, amines hydroxylamines or hydrazones to enones using different catalysts working under



Scheme 82 Two examples of aza-Michael reactions catalyzed by chiral thioureas.

H-bonding activation manifold but, in general, all methodologies suffer from low-or-moderate yields and/or poor enantioselectivities.[313]

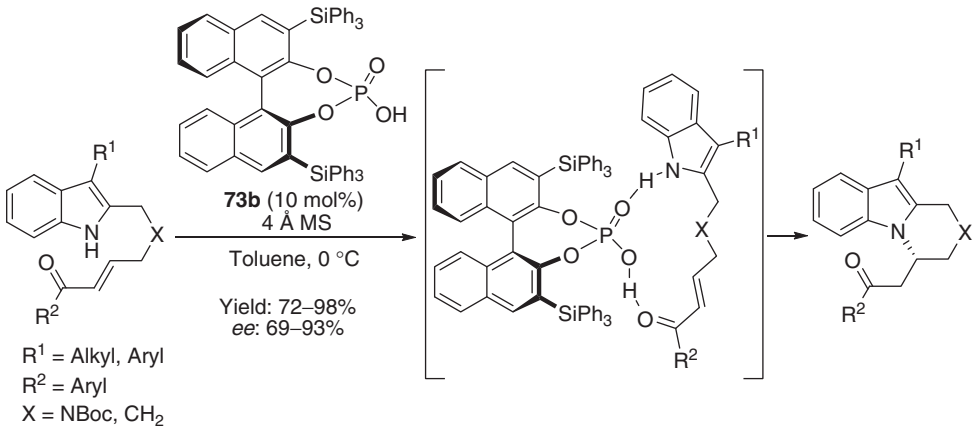


Scheme 83 The enantioselective conjugate addition of 2,4-dimethoxyaniline to nitroalkenes.

Finally, there is also one example of an intramolecular aza-Michael reaction proceeding under H-bonding catalysis in which a suitably substituted indole containing a side chain in which an α,β-unsaturated ketone moiety had been incorporated as the Michael acceptor, which underwent a clean reaction providing the corresponding tricyclic compounds in good yields and enantioselectivities (Scheme 84).[314] In this example, axially chiral phosphoric acid **73b** was identified as the best catalyst, which is proposed to be involved in a bifunctional behavior, by activating the enone through protonation whereas the P=O moiety would engage in the activation of the N-nucleophile Y, promoting the deprotonation of the indole moiety.

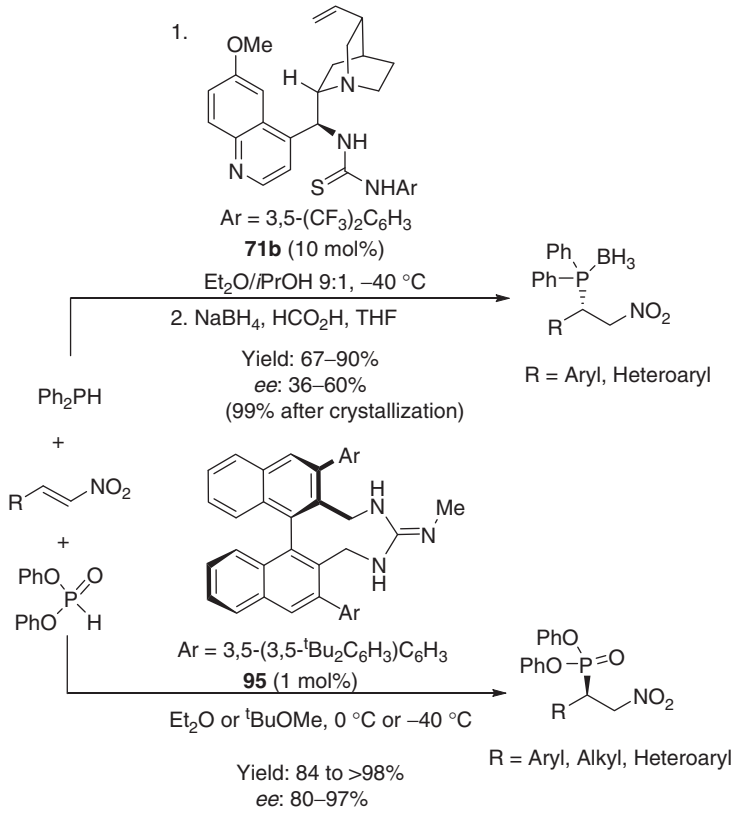
4.03.8.2.4 Phospha-Michael reaction

There are only a few examples of enantioselective conjugate additions of P-based heteronucleophiles under H-bonding catalysis, mostly focused on the use of nitroalkenes as Michael acceptors (Scheme 85). The addition of diphenylphosphine to a set of different β-aryl-substituted nitroalkenes was carried out using cinchona alkaloid-based thiourea **61b** as the catalyst,[315] the overall transformation involving the *in-situ* transformation of the phospha-Michael adducts by complexation with borane in order to prevent oxidation of the trisubstituted phosphine by ambient oxygen. Although enantioselectivities remained at values of approximately 65% *ee*, these could be improved to 99% *ee* in most cases after a single recrystallization process. Other reports have shown that diphenylphosphite can also be employed as a more stable and easy to manipulate phosphorous nucleophile.[316] Alternatively, chiral guanidines have also been successfully employed to catalyze this reaction and, for example, axially chiral



Scheme 84 Organocatalytic intramolecular aza-Michael reaction under H-catalysis.

guanidine **95** has been identified as an excellent catalyst that performs very well in terms of both chemical efficiency and enantioselectivity for a wide range of β-aryl- and β-alkyl-substituted nitroalkenes (Scheme 85).[317] In a different report, dihydroquinine has been used to catalyze the conjugate addition of diarylphosphines to chalcones furnishing moderate levels of enantiocontrol.[318]

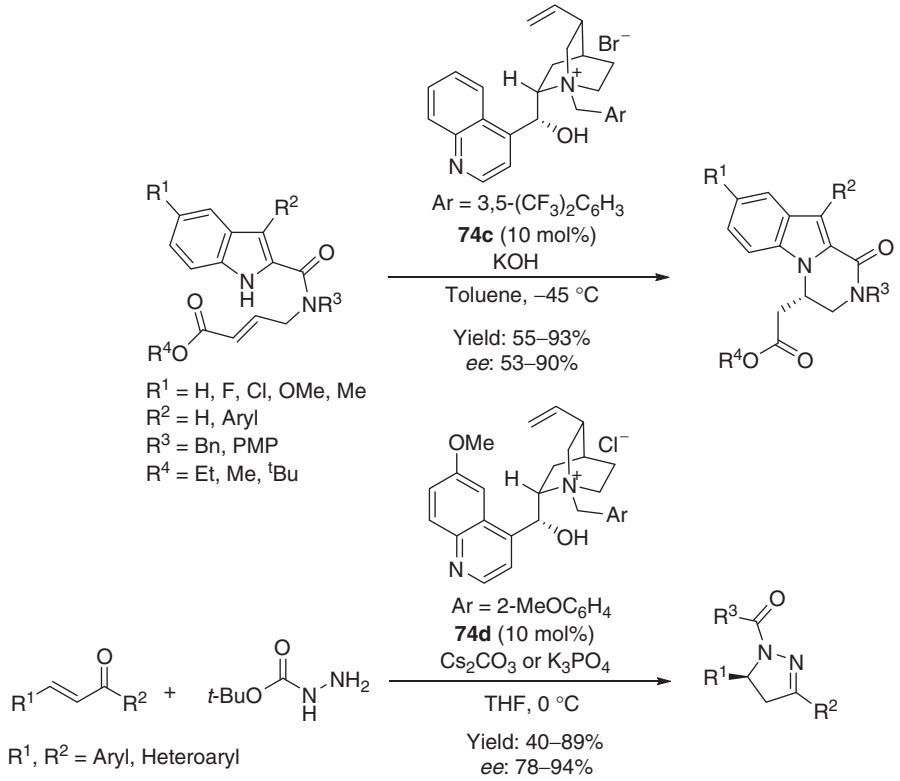


Scheme 85 Organocatalytic phospha-Michael reactions with nitroalkenes.

4.03.8.3 Phase-Transfer Catalysis

A couple of relevant examples of aza-Michael reactions carried out in an enantioselective manner by using a phase transfer catalyst have also been reported. In particular, an intramolecular aza-Michael reaction related to that presented in Scheme 86 using a functionalized indole derivative containing an α,β-unsaturated ester as an internal Michael acceptor has been described for accessing 1,2,3,4-tetrahydropyrazino[1,2-*a*]indoles.[319] Chiral ammonium salt **74c**, derived from cinchonidine, was used in the

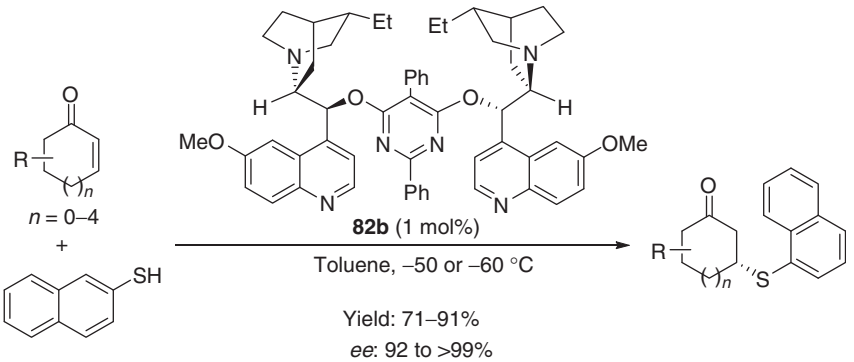
presence of an external base, such as KOH, leading to the formation of the final tricyclic compound in good yields and enantioselectivities of up to 93%. In a different approach, hydrazines were found to react with chalcones yielding pyrazolines after intramolecular hydrazone formation. Using catalyst **74d,** the final adducts were isolated in moderate-to-good yields and with good enantioselectivities when *tert*-butoxycarbonylhydrazine was used as the nucleophile (Scheme 86).[320] The reaction proceeded in the presence Cs_2CO_3 or K_3PO_4 as the external base in a solid–liquid mixture.



Scheme 86 Organocatalytic aza-Michael reactions under PTC conditions.

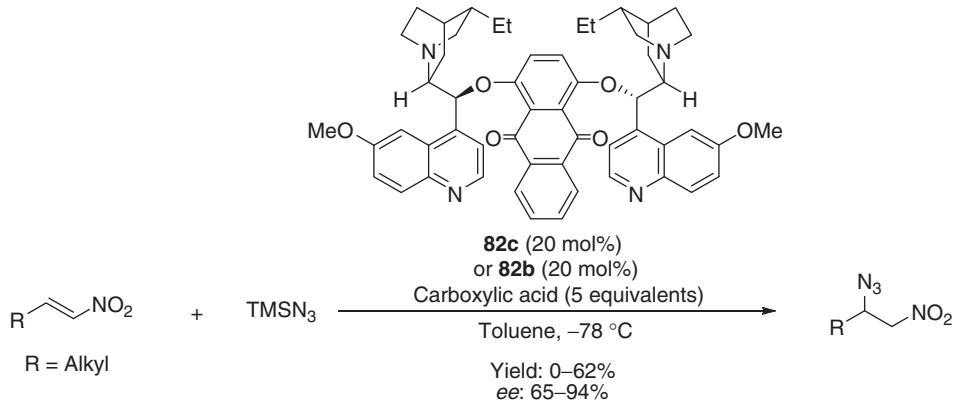
4.03.8.4 Brønsted Base Catalysis

A very effective methodology for carrying out the conjugate addition of arylthiols to cyclic enones has been reported using chiral dimeric cinchona alkaloid-based Brønsted base **82b** as catalyst (Scheme 87).[321] This protocol furnished the conjugate addition products in excellent yields and with very high levels of enantioinduction in almost all cases studied and using a remarkably low catalyst loading. The scope of the reaction was remarkably wide with respect to the cyclic enone substrate, obtaining good results regardless of its substitution pattern or ring size. On the contrary, the nature of the arylthiol employed was crucial for achieving a high stereocontrol, observing that 2-thionaphtol was the most appropriate Michael donor.



Scheme 87 Enantioselective sulfa-Michael reaction catalyzed by **82b.**

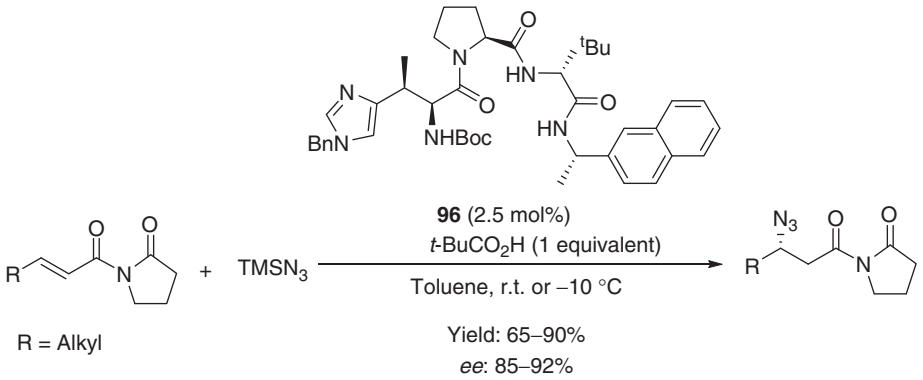
The possibility of carrying out the conjugate addition of the azide anion to nitroalkenes using the same type of Brønsted base catalysts has also been surveyed.[322] In this particular case, the commercially available dimeric cinchona alkaloid-based reagents $(DHQD)_2PYR$ **82c** and $(DHQD)_2AQN$ **82b** allowed the isolation of the final products with moderate-to-high enantiomeric excesses, although the yields remained moderate (Scheme 88). The reaction was performed at low temperatures in toluene to prevent racemization of the compound because of the strongly reversible character of the reaction. The authors selected $TMSN_3$ as the azide anion source, the nucleophile being generated in the reaction medium by the effect of a carboxylic acid like AcOH, benzoic acid, or other related reagents, which was incorporated in excess into the reaction scheme.



Scheme 88 Enantioselective aza-Michael reaction catalyzed by **82b** or **82c**.

4.03.8.5 Other Types of Catalysts

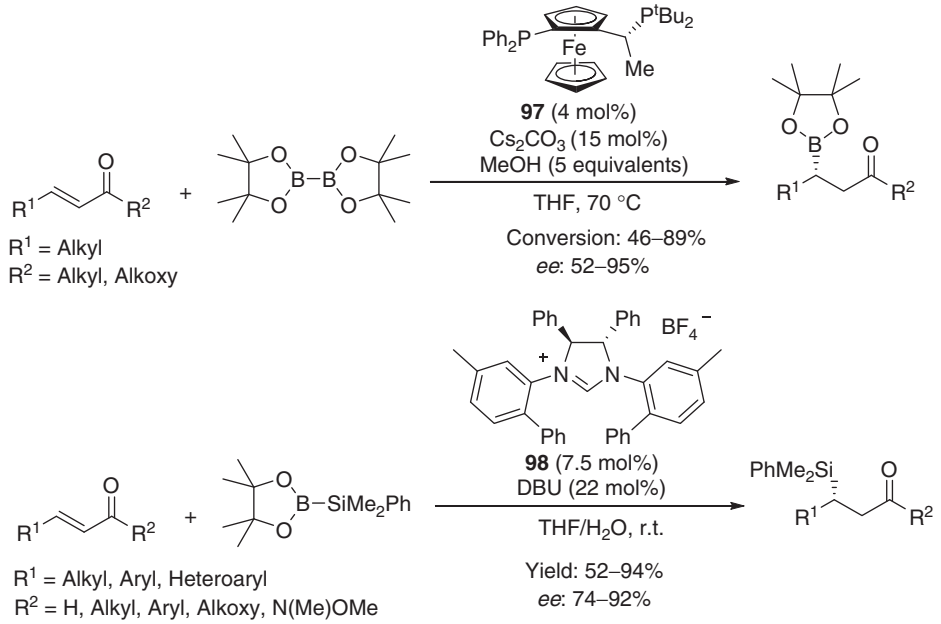
There are some other types of catalysts not covered in the previous sections, which have been applied to different types of hetero-Michael reactions, offering high levels of enantioselectivity in some cases. This is the case of the organocatalytic conjugate addition of azide to *N*-enoyl oxazolidinones catalyzed by a small peptide, which in fact represents one of the very early examples of an enantioselective aza-Michael reaction using organocatalysis and which proceeds with very high enantiocontrol.[323] In this reaction, trimethylsilyl azide was also employed as the azide source, which is generated by the effect of one equivalent of a carboxylic acid additive. The reaction proceeded successfully at room temperature or at $-10\ ^{\circ}C$, affording the final β-azidocarbonyl compounds in good-to-excellent yields and in very good enantioselectivities (Scheme 89). A very relevant and important feature associated with this reaction is the fact that it constitutes a very easy and straightforward approach to β-amino acids, which can be obtained after hydrogenation of the azide moiety followed by base hydrolysis. The proposed mechanism operating in the activation of the reagents by the peptide catalyst involves the formation of an internal H-bonding network within the catalyst structure, which stabilizes one particular conformation of the peptide, thereby generating a chiral pocket in which the reagents participating in the reaction are incorporated.



Scheme 89 Enantioselective conjugate addition of azide to enoyl oxazolidinones catalyzed by a chiral peptide.

In a completely different context, several groups have exploited the ability of Lewis bases to activate B–B and B–Si bonds in diboron or silylborane reagents, which can therefore participate as Michael donors in conjugate addition reactions, leading to the formation of the corresponding β-borylation/β-silylation products. This different activation mechanism involves the ability of

the Lewis base to interact with the Lewis acidic boron atom of the diboron or silylborane reagent, which induces a polarization of the B–B or B–Si bond thereby being able to react as a nucleophilic reagent in the presence of a suitable Michael acceptor.[324] In particular, chiral phosphine **97** has been reported to catalyze the β-borylation of enones and α,β-unsaturated esters with variable levels of conversion and enantioselectivities in the range of 52–95% *ee* (Scheme 90).[325] Alternatively, *N*-heterocyclic carbenes can also play the role of chiral Lewis bases in the reaction of bis(pinacolato)diboron with a wide variety of different Michael acceptors, which include cyclic and acyclic enones, and α,β-unsaturated esters, amides, and aldehydes with variable substitution patterns and with a rather wide functional group tolerance.[326] This situation has also been exploited to the conjugate addition of silyl groups to enones, enals, and α,β-unsaturated lactones, showing that the reaction using dimethylphenylsilylpinacolato boron as the source of the silicon nucleophile proceeds with excellent results in the presence of chiral NHC catalyst derived from imidazolium salt **98** (Scheme 90).[327]



Scheme 90 Enantioselective conjugate addition of boron and silicon nucleophiles to enones catalyzed by chiral Lewis bases.

4.03.9 Conclusions and Outlook

Organocatalytic conjugate addition reaction has undergone an impressive advance during the past few years, showing that organocatalysis can be employed as a powerful methodological approach for carrying out enantioselective conjugate addition reactions using a wide variety of nucleophiles and Michael acceptors, enabling the direct synthesis of a wide range of chiral compounds in a highly enantioenriched form. Several organocatalytic variants have been successfully employed for the conjugate addition of carbon, hydrogen, nitrogen, oxygen, phosphorus, and other atom-centered nucleophiles such as aminocatalysis, H-bonding catalysis, Brønsted base catalysis, phase transfer catalysis, catalysis based on carbenes and others. Furthermore, the applicability of the organocatalytic variants of conjugate addition reactions has already been shown by some examples directed toward the synthesis of some biologically active compounds or natural products. This is an area still open to new findings and contributions, presumably focused on the use of lower catalyst loadings and reaction times, wider scope of nucleophiles and acceptors, and new applications of these transformations in total synthesis or to the industrial production of fine chemicals. Therefore, new exciting progresses might be expected during the next years.

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4.04 Metal-Catalyzed Asymmetric Nucleophilic Addition to Electron-Deficient Alkenes

M Mauduit and O Baslé, Ecole Nationale Supérieure de Chimie de Rennes, Rennes Cedex, France
H Clavier, Aix Marseille Université, Marseille, France
C Crévisy and A Denicourt-Nowicki, Ecole Nationale Supérieure de Chimie de Rennes, Rennes Cedex, France

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Glossary

Enantioselective addition The combination of two achiral compounds to generate an optically active product.

Extended Michael acceptors Michael acceptors containing two or more conjugated multiple (double) bonds and consequently two or more reactive positions toward conjugate addition.

Friedel–Crafts conjugate addition reactions Alkylation of a (hetero)aromatic compound as a result of its 1,4-addition to electron-deficient alkenes.

Hard/soft nucleophiles Hard nucleophiles apply to species which are small with high charge density (e.g., alkylmetal species), whereas soft nucleophiles apply to species which are big with low charge density (e.g., malonate derivatives).

Michael addition This reaction corresponds to the nucleophilic addition of a β-dicarbonyl carbanion to an α,β-unsaturated carbonyl compound. This reaction belongs to the larger class of conjugate additions. By extension, the Michael addition also refers to the addition of various classes of carbanions or other nucleophiles.

Nucleophilic conjugate addition The addition of an electron-rich compound (nucleophile) to an electron-deficient alkene (or alkyne) conjugated with an electron-withdrawing function containing a multiple bond (e.g., carbonyl, nitro, nitrile, imine, etc.).

4.04.1 Introduction

In the field of modern asymmetric catalysis, the enantioselective 1,4- or 1,6-addition of various nucleophiles to electron-deficient alkenes represents one the most powerful method to form C–C or C-heteroelement bonds, which is widely used in total synthesis of complex chiral molecules.[1] This process, also referred as enantioselective conjugate addition (ECA), is the result of the formation of newly stereogenic centers, starting from prochiral substrates. In the first edition of *Comprehensive Organic Synthesis*, dated 1991, most of the cited works dealing with conjugate addition reactions described either noncatalyzed processes or nonenantioselective catalytic methods.[2] In fact, the metal-catalyzed enantioselective version was still in its infancy. Therefore, as this chapter will cover the metal-catalyzed ECAs, the major part of the disclosed works included within this chapter has been published after 1991.

In the last two decades, the development of new catalytic ECA methodologies has received tremendous attention. Significant breakthroughs were accomplished, notably through the design of new chiral nonracemic ligands and the evaluation of a large series of metal catalysts. These results allowed chemists to adapt, with more efficiency in terms of chemo-, regio-, and enantio-selectivity, this important organic synthetic reaction to a wide range of reagents (the nucleophiles on one side and the electro-deficient alkenes, usually referred as Michael acceptors, on the other side). Although organocuprates led naturally to the copper-catalyzed ECA as early as the 1990s – which remains a fruitful area today –, other metals have been progressively introduced (Ni, Pd, Rh, or lanthanoides). Thus, numerous challenging transformations were successfully achieved such as enantioselective addition of vinylic, alkynyl, silicon, and phosphorus nucleophiles; the formation of quaternary stereogenic centers or the addition to polyenic Michael acceptors. Less commonly used metals such as Ru, Ir, Cd, Fe, Zr, Hf, Zn, Mg, Co, Ca, Ba, Sr, and alkalis have also been studied over the past 20 years and have often led to interesting results. Some of these metal catalysts, like Fe and Ca, are particularly attractive for the development of more sustainable processes that takes into account the principles of 'green chemistry.'[3] Nowadays, the attention of the scientific community is focused on catalyzed enantioselective synthetic methodologies, which brings the most remarkable advances. Therefore, reports dealing with metal-catalyzed diastereoselective conjugate additions, where chiral nonracemic substrates are responsible for the control of the newly formed stereocenter, are not covered in this chapter.[4]

This chapter is divided into sections related to a metal or a metal family. Moreover, each section is organized by type of Michael acceptor families and by types of nucleophiles.

4.04.2 Copper-Catalyzed ECA

4.04.2.1 α,β-Unsaturated Enones

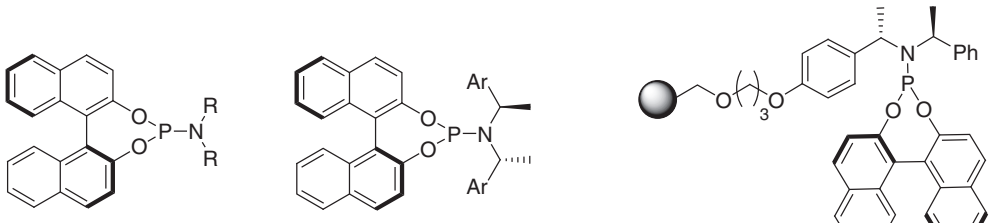
4.04.2.1.1 Addition of C-nucleophiles

4.04.2.1.1.1 Organozinc reagents

During the last two decades, tremendous attention has been given to copper-catalyzed asymmetric conjugate addition (ACA) of organozinc reagents to α,β-unsaturated ketones.[5] Since the first example described by Alexakis et al. in 1993,[6] this area of research has witnessed dramatic breakthroughs. Most of these developments were based on new ligand design, leading today to a profusion of chiral ligands able to offer with high efficiency and selectivity the addition of dialkylzinc reagents to a broad range of enone substrates. Among enone substrates, cyclohexenone offers numerous advantages and was generally considered as the substrate of choice for the evaluation of processes for copper-catalyzed enantioselective conjugated addition. In fact, cyclohexenone is reactive and cyclic (*cis*, *trans*-interconversion avoided). Although, cyclopentenone, which is also reactive and cyclic, suffers from its flatness and usually provides lower enantiomeric excess (*ee*).

4.04.2.1.1.1.1 Phosphoramidite ligands

Among the plethora of phosphorus-based ligands described in this field, phosphoramidites have concentrated a major part of the research attention (Figure 1).[7] In 1996, Feringa and coworkers described the first efficient ACA of dialkylzinc to cyclic and acyclic enones.[8] The reaction catalyzed by copper triflate and a binaphthyl-based phosphoramidite **L2** offered up to 90% *ee* with cyclohexenone. Subsequently, the intrinsic modularity of this easily prepared ligand family led to the characterization of a large ligand library.[9] Interestingly, the introduction of a chiral amine **L3** offered higher enantioselectivities for cyclohexenone-type substrates (up to >98%), whereas cycloheptenone and cyclopentenone offered only modest 53% and mediocre 10% *ee*, respectively (Scheme 1).[10] The potential of ligand **L3** and its isomers was evaluated in numerous transformations involving ACA of organozinc reagents, such as sequential reactions with cyclohexadienones (Scheme 2),[3,11] kinetic resolutions of substituted cyclohexenones (Scheme 3),[12] followed by epimerization.[13] Importantly, ligand **L3** also provided high enantioselectivities in the diphenylzinc addition to cyclohexenone.[14] In 2006, the naphthyl-substituted phosphoramidite **L4** was successfully employed as chiral ligand for the conjugated addition of Et_2Zn to α-halogenated cyclic enones.[15] In this report, Alexakis et al. demonstrated that the addition of styrene as radical scavenger improved enantioselectivity up to 98% *ee* (vs. 85% *ee* in the absence of styrene). Recently the replacement of the bis(1-phenylethyl)amine part by a chiral bis(1-ferrocenylethyl)amine offered high enantioselectivities (up to 98% *ee* with **L5**) for the addition of Et_2Zn to cyclic enones, including cycloheptenone (98% *ee*), whereas selectivities remained low for cyclopentenone and acyclic enones.[16] Immobilization of binaphthyl-based phosphoramidite ligands was first investigated in 2002 but provided only moderated enantioselectivity, while recycling was not described.[17] However, the anchoring of a **L3**-based phosphoramidite ligand onto a Merrifield resin (**L6**) provided up to 84% *ee* for the addition of diethylzinc with cyclohexenone with partial preservation of the selectivity in successive recycles.[18]



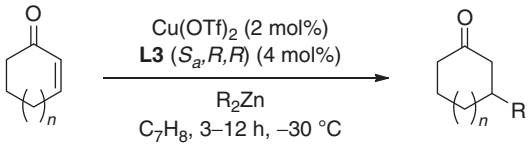
L1 (S_a,) R = Me
L2 (S_a,) R = *i*-Pr

L3 (S_a,*R*,*R*): Ar = Ph
L4 (S_a,*R*,*R*): Ar = 2-Naph
L5 (S_a,*R*,*R*): Ar = 1-Ferrocenyl

L6 (R_a,*S*,*S*)

Figure 1 Typical examples of binaphtyl-based phosphoramidite ligands.

Alexakis et al. have turned their attention onto the diol backbone of phosphoramidite ligand. The chiral binaphthol part was replaced by a racemic dynamic biphenol moiety for which the atropoisomerism is governed by the chiral amine. The clever and highly modular strategy led to the rapid evaluation and development of a large number of biphenyl-based phosphoramidite ligands **L7** achieving high enantioselectivities in the conjugated addition of Et_2Zn to a broad scope of cyclic and acyclic enones.[19] Introduction of the bulky chiral bis(1-naphtalenylethyl)amine allowed for further improvement in the addition of Et_2Zn to cyclohexenone (>99.5% *ee*) and cycloheptenone (>98% *ee*) (Scheme 4).[20] The diol backbone of phosphoramidite has witnessed



R =	Yield (%)	*ee*
Et	75	10

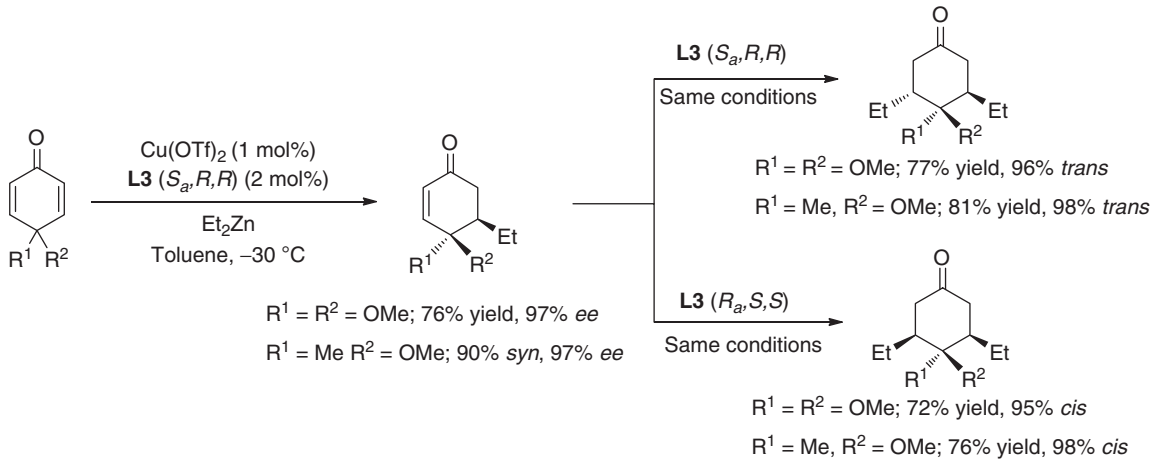
R =	Yield (%)	*ee*
Et	82	53

R =	Yield (%)	*ee*
Me	72	>98
Et	94	>98
Hep	95	95
i-Pr	95	94
$Ph(CH_2)_3$	53	95
$AcO(CH_2)_5$	77	95
$(EtO)_2CH(CH_2)_3$	91	97
$PivO(CH_2)_6$	87	93
Ph	>95	94

R =	Yield (%)	*ee*
Me	68	>98
Et	74	>98

R =	Yield (%)	*ee*
Et	93	>98

Scheme 1 Conjugated addition of organozinc reagents to cyclic enones with **L3.**



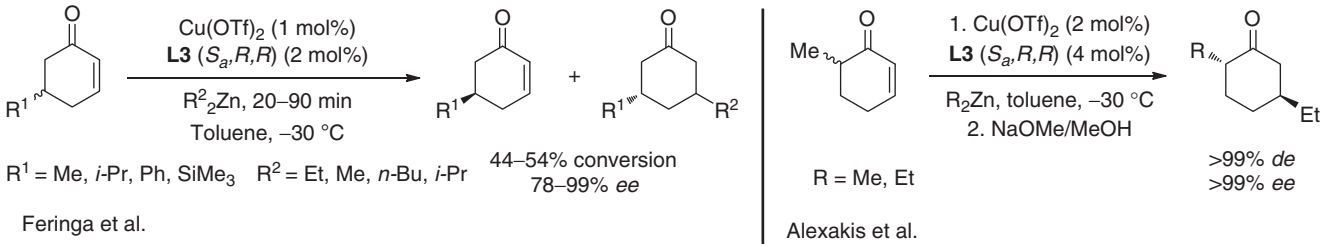
Scheme 2 Conjugated addition of organozinc reagents to cyclohexadienones with **L3**.

other modifications based on TADDOL[21] and more recently spiro-diol incorporation. TADDOL-based phosporamidites offered modest selectivities (up to 49% *ee* with **L8**), whereas diol ligand based on spirobiindane (**L9**)[22] and spirobixanthene (**L10**)[23] afforded excellent yields and enantioselectivties for the addition of Et_2Zn with cyclohexenone (up to 99% *ee*) and cycloheptenone (up to 98% *ee*) (Figure 2).

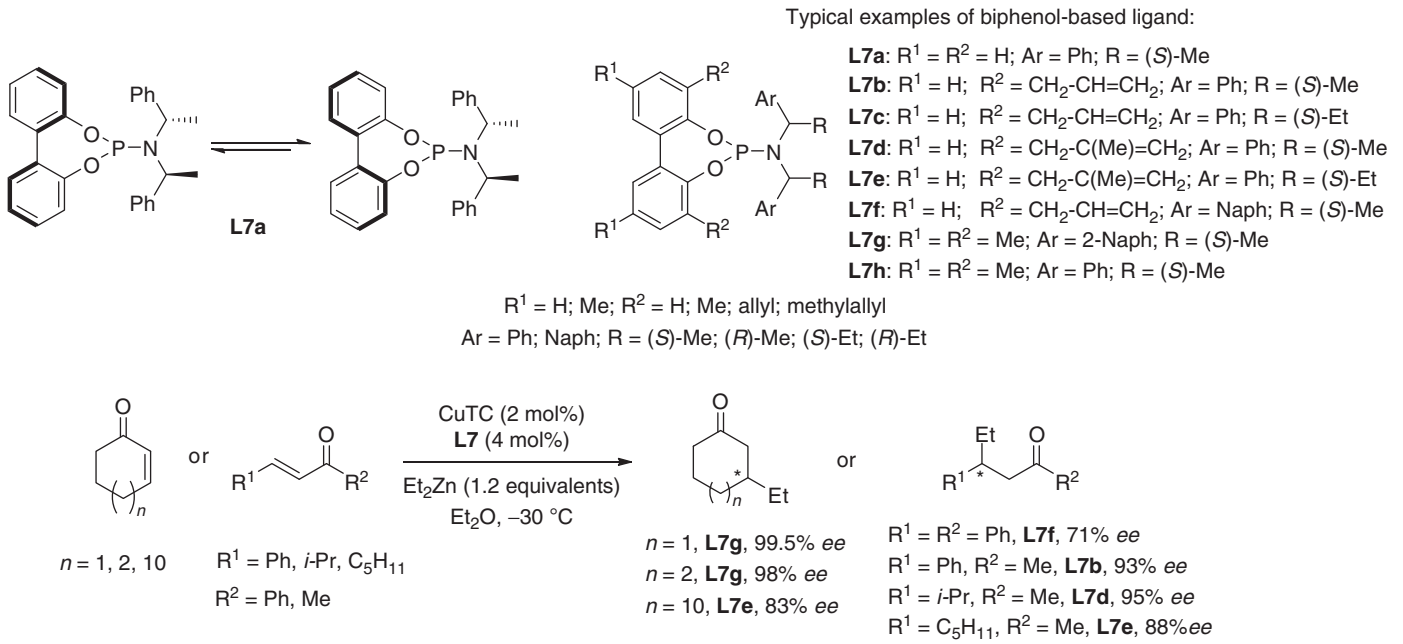
Recently, Zhang and coworkers reported new types of biphenyl phosphoramidite ligands containing a D_2-symmetric backbone. These ligands (**L11**) demonstrated high activity and selectivity with cyclic and acyclic substrates; up to 98% and 99% *ee* with cyclohexenone and chalcone, respectively (Scheme 5).[24]

4.04.2.1.1.1.2 Amino acid-based phosphine ligands

Readily modifiable chiral ligands facilitate the establishment of an appropriate enantioselective catalytic process.[25] In this context, Hoveyda et al. developed easily accessible peptide-based ligands providing high selectivity in copper-catalyzed conjugated addition of dialkylzinc reagents to α,β-unsaturated enones (Figure 3).[26] High enantioselectivities (≥95% *ee*) were observed in the presence of $Cu(OTf)_2{\cdot}C_6H_6$ and **L12a** for the addition of a broad range of organozincs, including poorly reactive Me_2Zn, to various five-, six-, and seven-membered ring cyclic enones.[27] Importantly, the obtention of high enantioselectivities (>90% *ee*) for conjugated addition with cyclopentenone constituted a veritable breakthrough. Moreover, acyclic aliphatic enones were also



Scheme 3 Kinetic resolution of substituted-cyclohexenones with **L3**.



Scheme 4 Biphenol-based phosphoramidite ligands in ACA with Et_2Zn and enones.

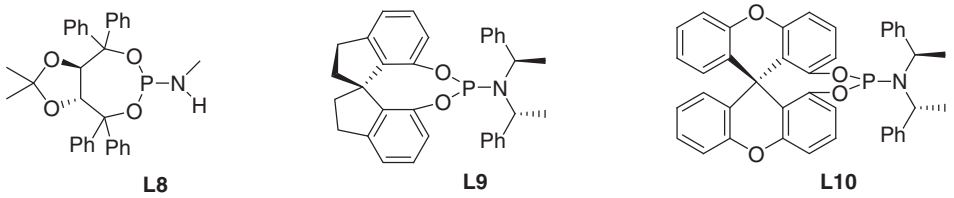
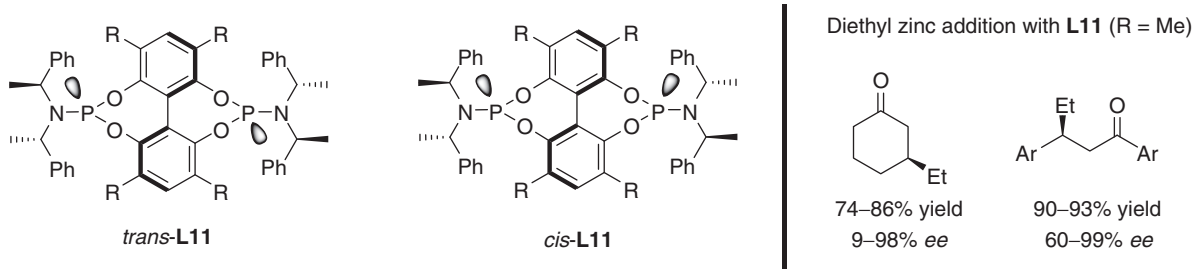


Figure 2 TADDOL and spiro phosphoramidite ligands.



Scheme 5 D_2-symmetric of biphenyl phosphoramidite ligands.

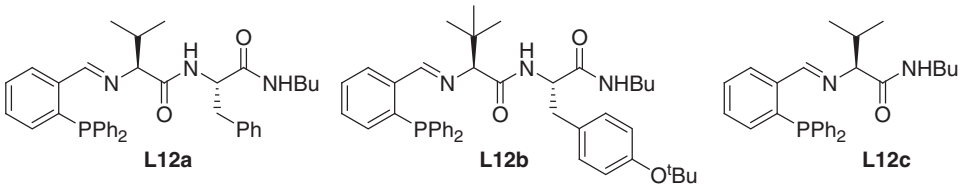
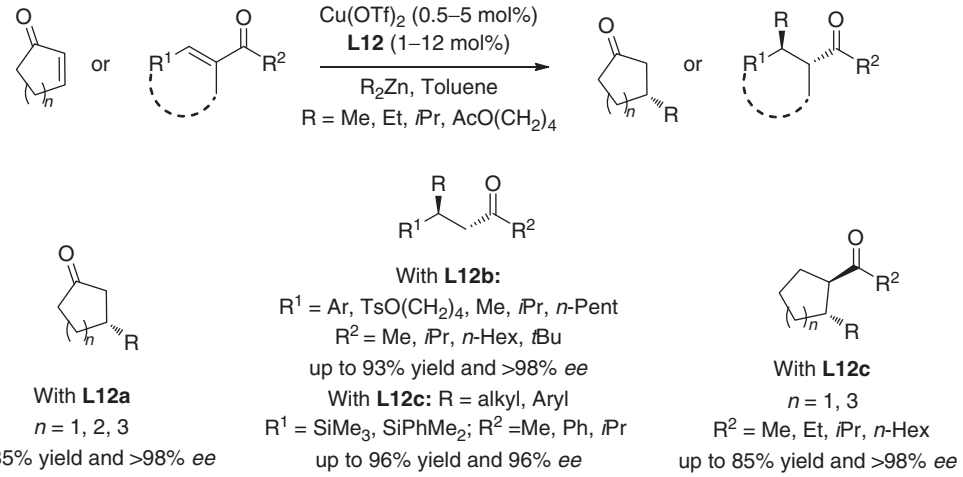


Figure 3 Typical amino acid-based phosphine ligands.

efficiently employed in the copper-catalyzed conjugated addition of Et_2Zn and Me_2Zn with ligand **L12b** affording excellent level of activity and enantioselectivity (up to 95% *ee*).[28] Interestingly the reaction with more substituted cyclic alkenes, with the exception of cyclohexenyl substrates which are inert to catalytic ACA conditions, was efficiently promoted by the phosphine-amino acid-based ligand **L12c** with similar asymmetric induction.[29] The valine-based ligand **L12c** was later efficiently used in the preparation of chiral allyllsilanes[30] and a total synthesis of erogorgiaene (Scheme 6).[31]



Scheme 6 Amino acid based-phosphine ligands in ACA to cyclic and acyclic enones.

In parallel, different types of amino-acid based phosphine ligands were also evaluated in the ACA of dialkylzinc reagents to α,β-unsaturated ketones (Figure 4). The combination of 2 mol% of $Cu(OTf)_2$ and 3 mol% of ligand **L13** allowed the conjugated

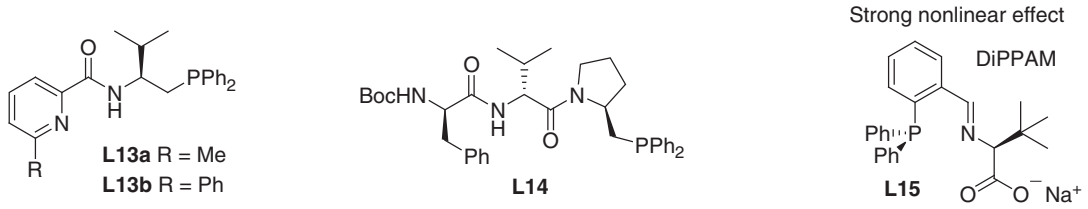


Figure 4 Other types of amino acid-based ligands.

addition of diethylzinc to cyclohexenone, cycloheptenone, and chalcone with good yield and enantioselectivity (up to 87% *ee*).[32] In 2007, Tomioka and coworkers developed a new peptidic amidomonophosphane ligand **L14** for the copper-catalyzed conjugated addition of dialkylzinc to cyclic enones.[33] High enantioselectivity (up to 98% *ee*) was achieved for the diethyl- and diisopropylzinc addition to cyclohexenones catalyzed by $Cu(MeCN)_4BF_4$, whereas moderate enantiocontrol was observed for dimethylzinc addition (45% *ee*). Kinetic resolution reaction of racemic 5-substituted cyclohexenones via copper-catalyzed diethylzinc addition using ligand **L14** afforded 3,5-disubstituted cyclohexanones (up to 90% *ee*) along with the enantioenriched starting material (up to 98% *ee*).[34] Ligand **L14** was later evaluated in a two-step asymmetric synthesis of *trans*-2,5-disubstituted cyclohexanones.[35]

Recently, Mauduit and coworkers evidenced strong positive nonlinear effect (NLE) in the copper-catalyzed conjugated addition of dialkylzinc to α,β-unsaturated ketones in the presence of the *t*-butyl DiPPAM ligand (**L15**).[36] As a representative example, the addition product of diethylzinc to cyclohexenone was obtained with 83% *ee* with a ligand possessing only 40% *ee*. Of note is that this catalytic system also provided high enantioselectivity with both cyclic (up to 98% *ee*) and acyclic enones (up to 97% *ee*).[37]

4.04.2.1.1.1.3 NHC-ligands

In 2001, the diaminocarbene ligand demonstrated strong potential in the conjugated 1,4-addition of diethylzinc to α,β-unsaturated ketones.[38] Despite the high activity and regioselectivity observed with both cyclic and aliphatic enones, the asymmetric induction with chiral *N*-heterocyclic carbene (NHC) ligands **L16–18** was low (up to 51% *ee* with cycloheptenone).[39] The library of C_2-symmetrical chiral NHC ligands was then extended to **L19–21** and afforded improved enantioselectivies but reaching still with difficulty the 90% *ee* level (low (69% *ee*) with cyclohexenone and up to 93% *ee* with cycloheptenone).[40] Amino-alcohol-based bidentate NHC ligands were then introduced,[41] and after extensive library screening, **L22** evidenced better selectivities in the conjugated addition of diethylzinc to cyclic enones (up to 92% *ee* with cyclohexenone).[42,43] Recently, hydroxy-amide azolium as precursors for NHC ligand demonstrated interesting selectivities with cyclic[44] and acyclic enones.[45] The amide function of ligand **L23** provided an additional coordination site increasing potentially facial selection, whereas lower enantiocontrol was observed with the C_2-symmetric bis(hydroxyamide) azolium ligand (Figure 5).[46]

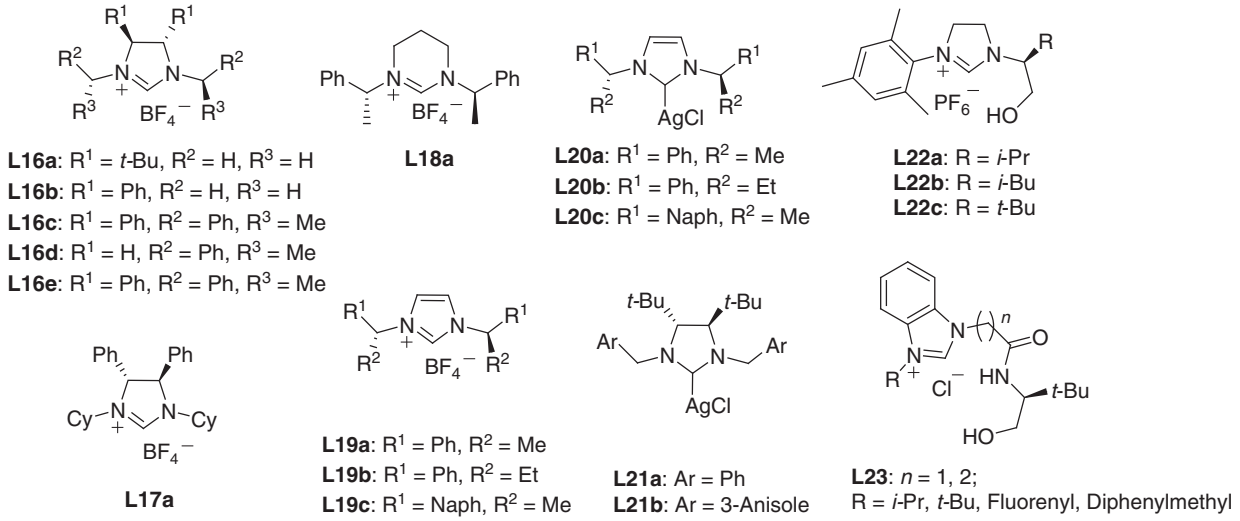
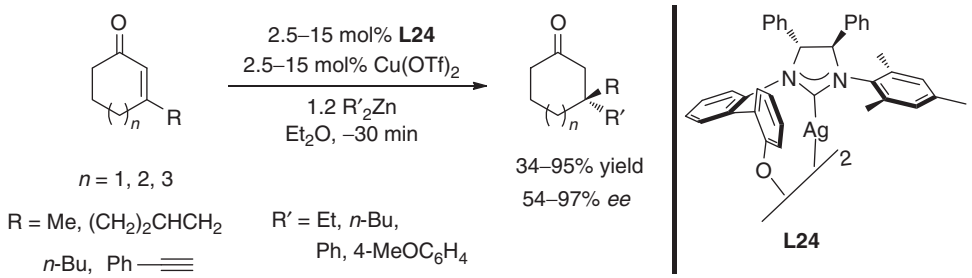


Figure 5 Chiral NHC ligands for Cu-catalyzed ACA.

Additionally, hydroxy-chelating diaminocarbenes based on the chiral Corey's 1,2-diamine and biphenol were employed in the conjugated addition to β-substituted cyclic enones for the construction of all-carbon quaternary centers. Using 2.5–15 mol% $Cu(OTf)_2{\cdot}C_6H_6$ and NHC ligand **L24**, the dialkyl- and diarylzincs were efficiently reacted with high enantioselectivities (Scheme 7).[47]



Scheme 7 Cu/NHC-catalyzed all-carbon quaternary centers with dialky- and diarylzinc nucleophiles.

4.04.2.1.1.1.4 Phosphine-based ligands

The binaphthyl scaffold has proved to be an excellent framework for the construction of chiral ligands, particulary phosphine-based ligands (Figure 6). In 1999, Zhang and coworkers achieved high enantioselectivity with the tridentated *P,N,N* ligand **L25** for Cu-catalyzed conjugate diethylzinc addition to cyclic (92% *ee* with cyclohexenone) and acyclic enones (up to 98% *ee* to chalcones derivatives).[48] A similar level of enantiocontrol was obtained for the diethylzinc addition to chalcone and benzylideneacetone substrates with both chiral ligand **L26** based on the atropoisomery of the biphenyl backbone,[49] and ligand **L27** incorporating *N*-sulfonamide function.[50] In 2005, the phosphino-naphthol ligand **L28** demonstrated excellent enantioselectivity in the conjugated addition of diethylzinc to acyclic enones (up to >99% *ee*). Interestingly, reactions in both *N,N*-dimethylformamide (DMF) and toluene as solvent showed a negative NLE with ligand **L28**. Later Morimoto et al. developed an efficient *P,O,N* ligand (**L29**) for copper-catalyzed conjugated addition of diethylzinc to cyclohexenone (up to 99% *ee*).[51] In 2010, Endo and coworkers discovered that the binol **L30** scaffold coordinated to multiple metal centers resulted in a highly efficient enantioselective conjugated addition of diethylzinc to acyclic enones (up to 99% yield and >98% *ee*).[52] Recently, the same group observed a dramatic effect of regioisomeric ligands (**L32** and **L33**) providing the diethylzinc addition products with high enantioselectivity and opposite optical rotations.[53]

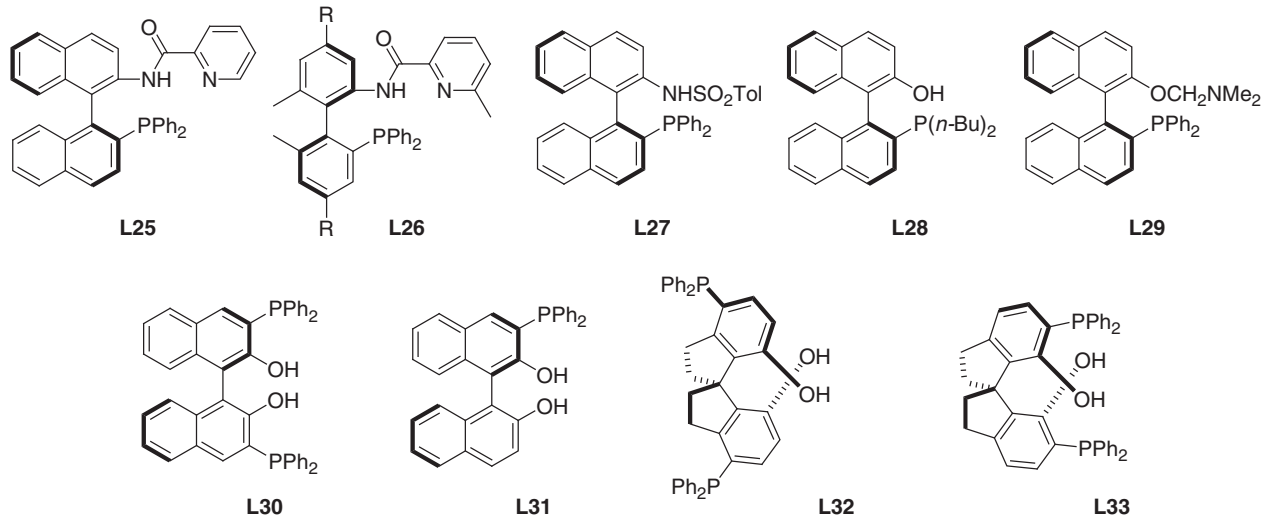


Figure 6 Atropoisomery-based chiral phosphine ligands.

In 1999, Imamoto described the synthesis of the P-chiral ligand (MiniPhos **L34**).[54] Later, P-chiral *o*-phosphinophenol **L35** and phosphinoanisole **L36** appeared as efficient bidentate ligands for copper-catalyzed conjugated addition of diethylzinc to chalcones substrates (up to 96% *ee*).[55] In 2006, high enantioselectivity levels were achieved in the presence of ferrocenyl-phosphine *P-N* ligand **L37** (up to 92% *ee*).[56] Interestingly, Wang and coworkers observed a dramatic improvement of selectivity with chalcones bearing *ortho*-substituents. In a practical manner, Leighton and coworkers introduced an efficient *P-N* ligand **L38** furnishing high enantioselectivity for diethylzinc addition to cyclic enones (up to 97% *ee* with cyclohexenone). Remarkably, no alteration of the enantiocontrol was observed on a large-scale reaction (10 g, with 0.1 mol% catalyst).[57] Nevertheless, the additional coordination site afforded by ligand **L39** was necessary to achieved high enantioselectivity with more challenging acyclic enones.[58] Indeed, the tridentate phosphine-amino alcohol **L40** provided the desired conjugated addition products of both diethyl- and dimethylzinc addition to acyclic enones with very high enantioselectivity (up to >98% *ee*).[59] In 2008, high levels of enantiocontrol were also obtained with acyclic enones and the tridentate *P,N,O* ligand **L41**.[60] The same year, Hayashi and coworkers described a new type

of *P,N,N* ligand starting from chiral amino-alcohols.[61] The tridentate ligand **L42** afforded modest to excellent enantiomeric excess for the ACA of dialkylzinc to cyclic enones and moderate yield and enantiocontrol was observed with the chalcone substrate (up to 52% yield and 62% *ee*). In 2002, Shintani and Fu obtained high enantioselectivities in the conjugated addition of diethylzinc to chalcone derivatives and achieved up to 91% *ee* with the chiral phosphaferrocene ligands **L43**.[62] A similar level of enantiocontrol was observed with the chiral phosphanylferrocenecarboxamide chiral ligands **L44**.[63] Recently, Dogan et al. tested phosphino ferrocenyl aziridinyl methanol ligands and obtained high yields and enantioselectivities in the conjugated addition of diethylzinc to acyclic enones with ligand **L45** (up to 96% yield and up to 92% *ee*) (Figure 7).[64]

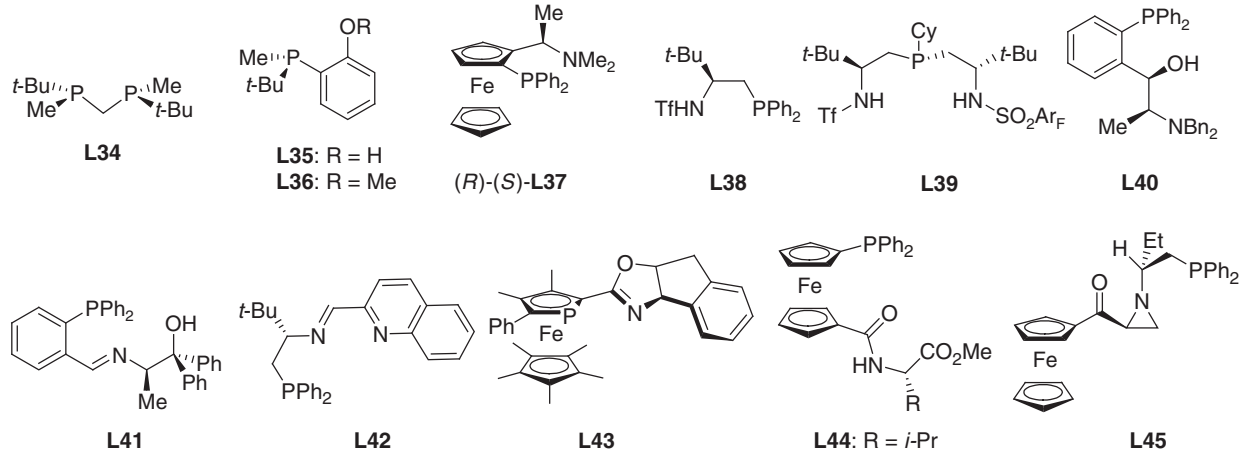


Figure 7 Other chiral phosphine ligands.

4.04.2.1.1.1.5 Phosphite ligands

In 1997, Alexakis et al. described the copper-catalyzed enantioselective conjugated addition of diethylzinc to cyclohexenone, benzalacetone, and chalcone using phosphites as chiral ligands.[65] Numerous phosphite ligands combining different chiral motifs such as menthol, borneol, ephedrine, tartrate, C_2 symmetrical diols, and binaphthol were evaluated. Despite the relatively low enantiomeric excess (up to 65% *ee* with benzalacetone and **L46**), the results provided a better understanding of the enantiocontrol. Monophosphite ligand incorporating the TADDOL motif and an additional exocyclic chiral group can provide high enantioselectivities. Indeed, Alexakis and coworkers achieved up to 96% *ee* in the conjugated addition of diethylzinc to cyclohexenone with ligand **L47**.[21] Nevertheless, subsequent developments with monodentate monophosphite binaphthol-based ligands only provided modest to good enantioselectivities.[66–68] Notably, ligands **L48** and **L49** were employed in the asymmetric preparation of (*R*)-muscone (up to 68% yield and 78% *ee* with **L49**) via the dimethylzinc addition to (*E*)-cyclopentadec-2-en-1-one (Figure 8).

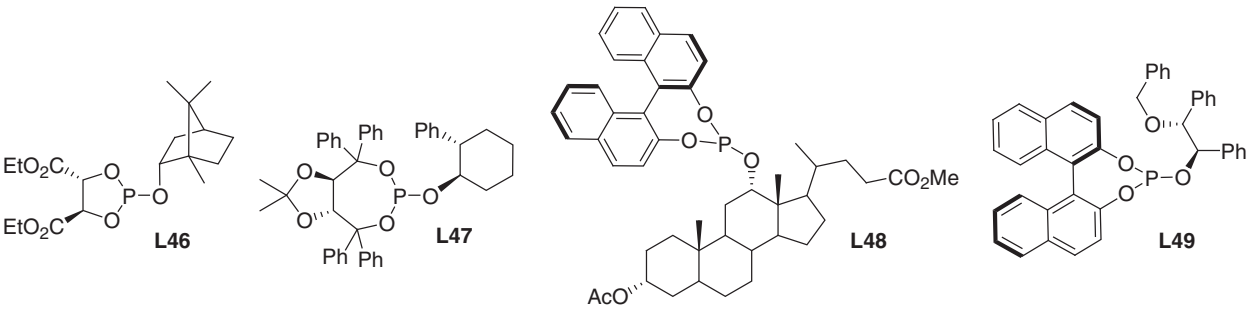


Figure 8 Monodentate monophosphite ligands.

However, Chan and coworkers achieved high enantioselectivity (>90% *ee*) in the conjugated addition of diethylzinc to cyclohexenone using bidentate diphosphite ligand **L50** based on the binaphthol scaffold.[69,70] Later, simple modifications of the reaction conditions with ligand **L50a** afforded higher enantioselectivity (up to 98% *ee*).[71] Excellent results (up 99% yield, up to 99% *ee*) were obtained with ligands **L51** derived from H8-binaphthol in the conjugated addition of dialkylzinc addition to cyclohexenone, cyclopentenone, and cycloheptenone (Figure 9).[72]

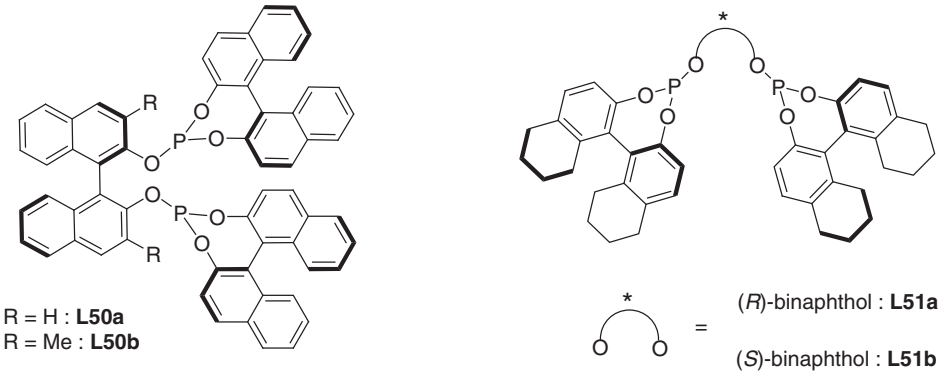


Figure 9 Bidentate diphosphite ligand based on the binaphthol scaffold.

Chiral diphosphite ligands **L52–L53** derived from pyranoside backbones of glucose and galactose were tested in the conjugated addition of diethylzinc addition to cyclic enones and afforded up to 88% *ee* with cyclohexenones.[73] Only moderate enantioselectivity was obtained with glucosamine **L54** (up to 64% *ee*),[74] D-xylose,[75] and mannitol-based diphosphite ligands **L55** (up to 71% *ee*).[76] Recently, higher enantiocontrol was observed with mannitol-based diphosphite incorporating H8-binaphthol motif (up to 93% *ee*) (Figure 10).[77]

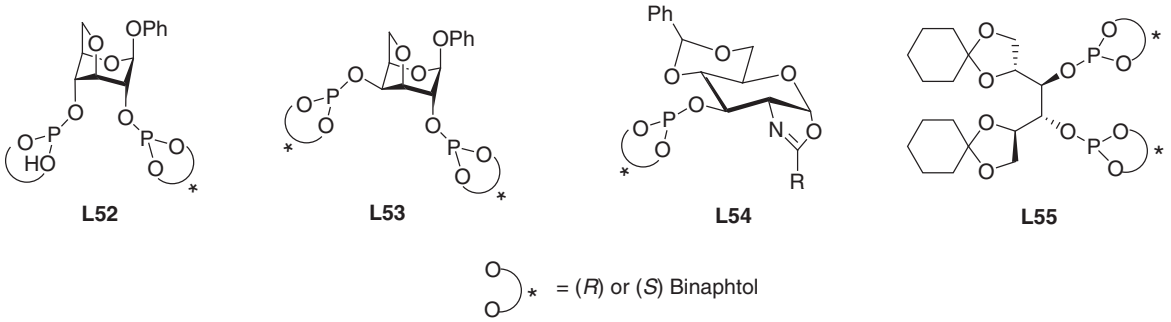


Figure 10 Sugar-based phosphite ligands.

4.04.2.1.1.1.6 Phosphite–pyridine ligands

In 2003, Hu and coworkers developed chiral bidentate phosphite–pyridine ligands **L56** incorporating the binaphthol motif. High enantioselectivity was achieved for the conjugated addition of diethylzinc to chalcone substrates (up to 97% *ee*), whereas only modest enantiocontrol was observed with cyclohexenone (53% *ee*).[78] The same level of selectivity could be obtained with the biphenyl-based phosphite ligand **L57** and chalcone substrates.[79] Evaluation of the diastereomeric ligand **L58** in the conjugated addition of diethylzinc to chalcone afforded up to 96% *ee*.[80] Recently, the same group synthesized a new class of modular pyridine–phosphite ligands **L59** able to reach the 90% *ee* level in the conjugated addition of diethylzinc to chalcone substrates (Figure 11).[81]

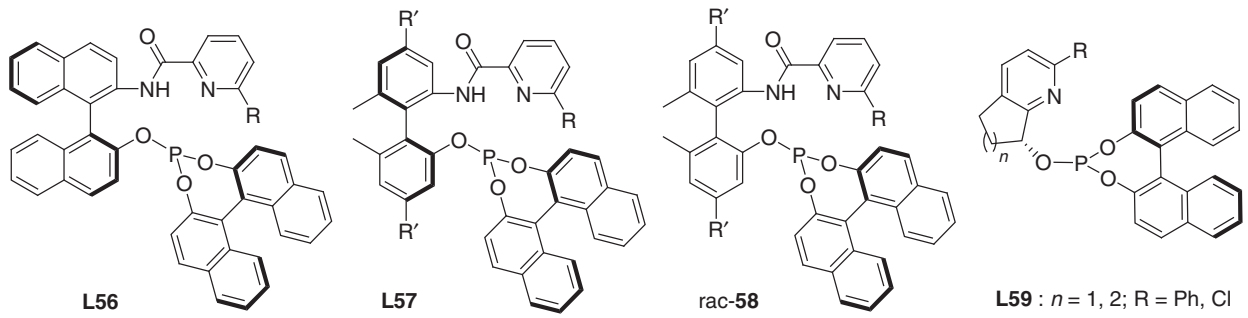


Figure 11 Bidentate phosphite-pyridine ligands.

4.04.2.1.1.1.7 Phosphinamine ligands (SimplePhos)

Recently, Alexakis and coworkers introduced a new type of phosphorus-based chiral ligand for copper-catalyzed conjugated addition of organometallic reagents (Figure 12). The modularity of these SimplePhos ligands allows for easy structure variations and the induced helicity promoted by the chiral amine part afforded up to 95% *ee* for the conjugated addition of diethylzinc to cyclohexenone with **L60a**.[82] Good enantioselectivity (up to 80% *ee* with **L60b**) was also observed with acyclic enones.[83]

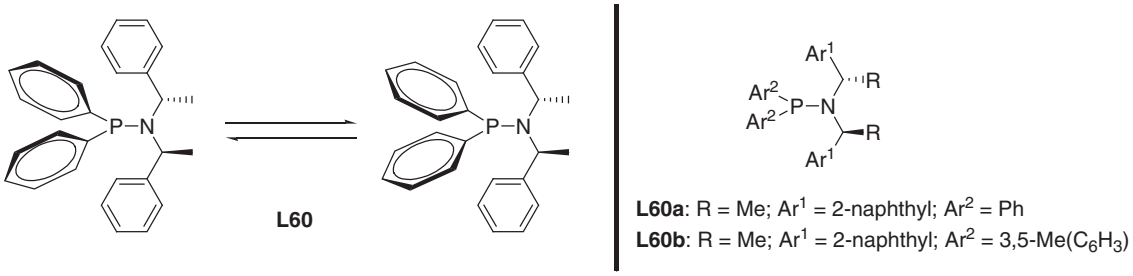


Figure 12 SimplePhos ligands.

4.04.2.1.1.1.8 Phosphonite ligands

In comparison with phosphite ligands, phosphonites with a carbon atom linked to the phosphorus center have received less attention. TADDOL[17] and binaphthol[84] based phosphonite ligands (**L61** and **L62**) afforded modest to moderate enantioselectivities for the conjugated addition of diethylzinc to cyclic enones. However, high enantioselectivities were achieved with ligand **L63** combining two binaphthol motifs on a ferrocene backbone (up to 95% *ee* with cyclohexenone) (Figure 13).[85]

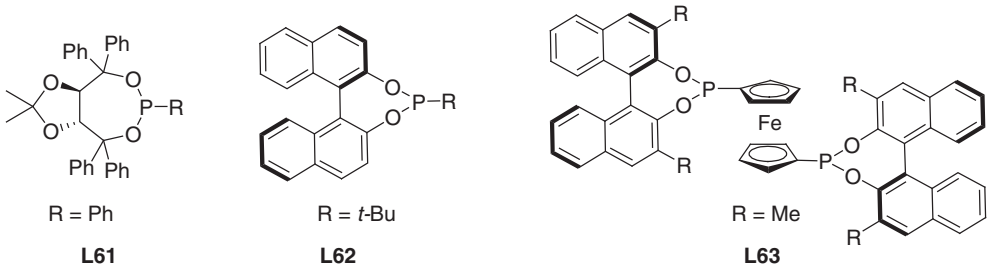


Figure 13 Phosphonite ligands for copper-catalyzed conjugated addition of dialkylzinc.

4.04.2.1.1.1.9 Miscellaneous phosphorus ligands with mixed functionalities

An efficient mixed function association is represented by the bidentate phosphite-oxazoline ligand **L64** described in 1997 by Pfaltz and coworkers and with which up to 96% *ee* was achieved for the conjugated addition of dimethylzinc to cyclohexenone.[86] Phosphoramidite incorporating an additional coordination site was also evaluated in the conjugated addition of dialkylzinc to enones. The best result for bidentate amino-phosphoramidite ligands was obtained with the chiral ligand **L65** that achieved moderate enantioselectivities for the 1,4-addition of diethylzinc to cyclohexenone.[87] Higher enantiocontrol was obtained with mixed phosphoramidite-phosphite ligands **L66** (up to 90% *ee* with cyclohexenone) (Figure 14).[88]

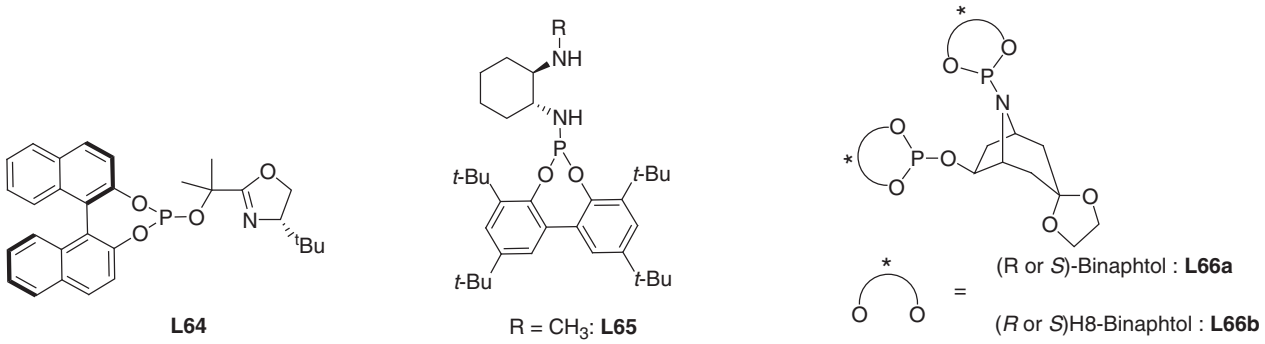
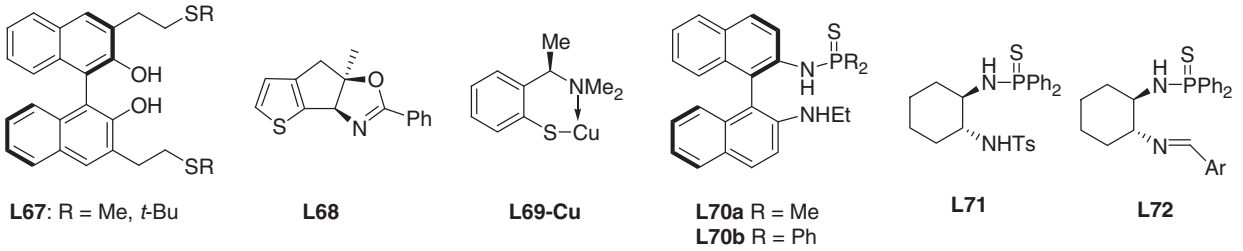


Figure 14 Miscellaneous phosphorus ligands.

4.04.2.1.1.1.10 Sulfur-containing ligands

In 1999, Woodward and coworkers demonstrated that thiobinaphthol-based ligands can induce modest enantioselectivity in the conjugated addition of organometallics, such as diethylzinc to cyclic and acyclic enones.[89] Later, good to excellent enantioselectivities were obtained for the conjugated addition of diethylzinc to cyclic and acyclic enones with thio-substituted-binaphthol ligand **L67** (85–96% *ee*).[90] Another type of ligand based on an oxazoline motif afforded modest to good enantioselectivties in the 1,4 addition of diethylzinc to chalcones (up to 79% *ee* with ligand **L68**).[91] The copper complex **L69**-Cu developed by Van Koten and coworkers provided good enantioselectivities in the conjugated addition of diethyl zinc to cyclic and acyclic enones (up to 83% *ee*) with interesting positive NLEs.[92] Shi et al. developed a thiophosphoramide ligand and evidenced the large potential of this new bidentate *S*,*N*-type ligand in the conjugated addition of diethylzinc to both cyclic and acyclic enones. Indeed, the catalytic system based on **L70** afforded after optimization, 95% *ee* with cyclohexenone, 98% *ee* with cyclopentenone, 97% *ee* with cycloheptenone, and up to 97% *ee* with acyclic chalcone. Interestingly, the presence of the sulfur atom was demonstrated to be crucial because its replacement by an oxygen atom shows no enantioselectivity.[93] The same group described other types of chiral bidentate thiophosphoramide ligands **L71**[94] and **L72**[95] that provided moderate to good enantioselectivity (up to 90% *ee*) in the 1,4 addition of diethylzinc to cyclic enones (Figure 15).

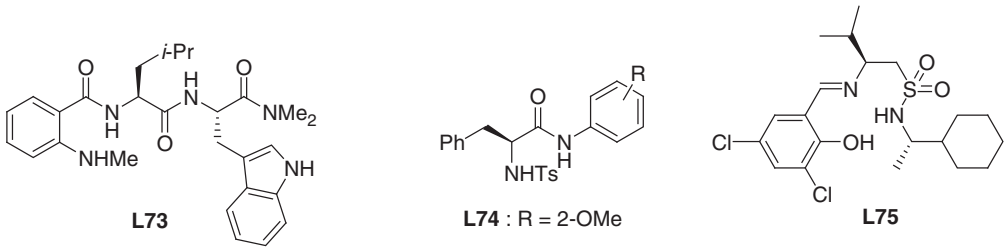


L67: R = Me, *t*-Bu **L68** **L69-Cu** **L70a** R = Me **L70b** R = Ph **L71** **L72**

Figure 15 Sulfur-containing ligands.

4.04.2.1.1.1.11 Nonphosphorus amino acid-based ligands

Hoveyda and Hird investigated nonphosphorus peptide-based ligands in the conjugated addition of dialkylzinc reagents to tetrasubstituted cyclic enones. High activities and enantioselectivities were achieved for the construction of chiral quaternary centers (up to 95% *ee* with **L73**), whereas only racemic products were obtained in presence of the previously described phosphorus-based ligand.[96] Recently, another class of amino acid-based chiral ligands synthesized from L-phenylalanine was evaluated in the copper-catalyzed ACA of diethylzinc to cyclic enones. The best result was obtained with ligand **L74**, affording moderate 72% *ee* with cyclohexenone. It is important to note that the latest were designed to mimic *β*-amino sulphonamide-based ligand **L75** developed by Gennari and coworkers, and for which up to 90% *ee* was achieved in the diethylzinc conjugated addition to cyclohexenone (Figure 16).[97]



L73 **L74** : R = 2-OMe **L75**

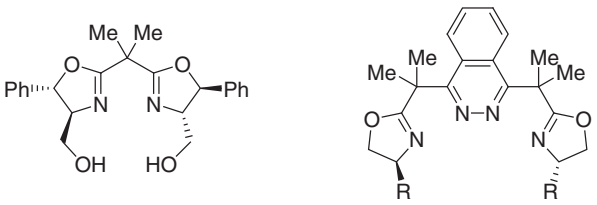
Figure 16 Nonphosphorus amino acid-based ligands.

4.04.2.1.1.1.12 Bis(oxazoline) ligands

In 2001, Reiser and coworkers demonstrated that bis(oxazoline) chiral ligands having hydroxymethylene side chains can be employed with efficiency in the conjugated addition of dialkylzinc reagents. Indeed, ligand **L76** appeared particularly efficient and provided up to 94% *ee* for the diethylzinc addition to cyclic enones.[98] Recently, Zhang and coworkers achieved good to excellent enantioselectivities for the 1,4-addition of diethylzinc to acyclic enones (up to 95% *ee*). Based on 1H NMR analysis, ligand **L77** possessing two equivalents coordination sites was assumed to undergo a bimetallic catalytic process (Figure 17).[99]

4.04.2.1.1.2 Organomagnesium reagents

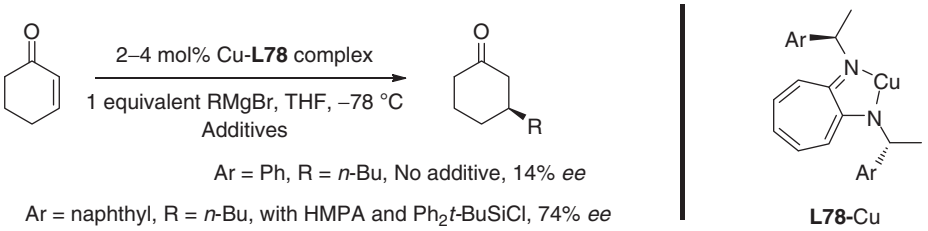
When taking into account atom economy, availability, low cost and toxicity, Grignard reagents are probably more valuable nucleophiles than their organozinc and organoaluminum equivalents.[100] In 1988, Lippard and coworkers reported the first



L76 **L77**: R = Ph

Figure 17 Bis(oxazoline) ligands.

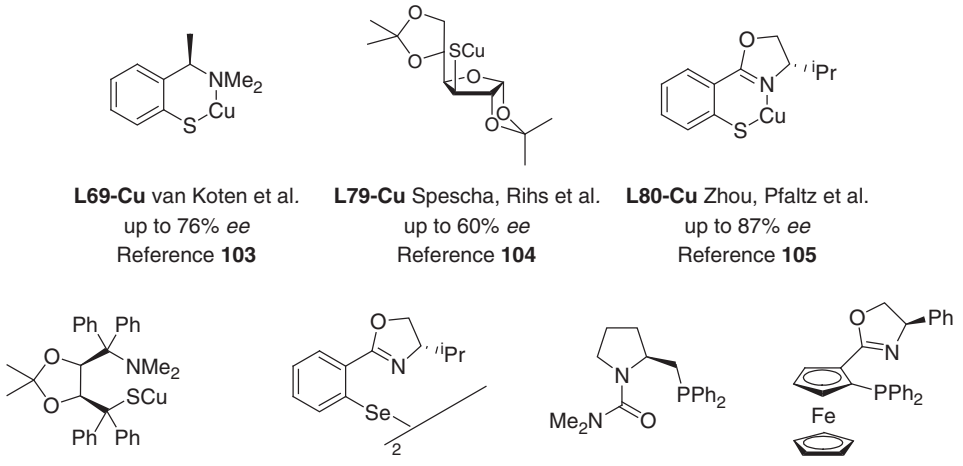
example of copper-catalyzed ACA of Grignard reagents (Scheme 8).[101] In this pioneering report, enantioselectivity (up to 14% *ee*) was obtained for the conjugate addition of *n*-BuMgBr to cyclohexenone catalyzed by CuBr·SMe_2 and a *N,N′*-dialkyl-substituted aminotroponeimine-based chiral ligand. Soon after, the same group demonstrated that a significant increase in enantioselectivity occurred in the presence of hexamethylphosphoramide (HMPA) and silyl reagents to offer up to 74% *ee* for the selective addition of *n*-BuMgCl to cyclohexenone.[102]



L78-Cu

Scheme 8 First examples of copper-catalyzed enantioselective conjugated addition with Grignard reagents.

Subsequent developments were based on copper complexes with chiral thiolates **L69–Cu, L79–L82**–Cu[103–107] and chiral phosphine **L83–L84**[108,109] ligands. Nevertheless, the reaction appeared highly sensitive to the reaction conditions with limited scope and rarely reached the 90% enantiomeric excess level (Figure 18). Therefore, almost 15 years of intensive research were necessary to achieve an efficient system for Cu-catalyzed ACA with organomagnesium reagents.



L69-Cu van Koten et al.
up to 76% *ee*
Reference **103**

L79-Cu Spescha, Rihs et al.
up to 60% *ee*
Reference **104**

L80-Cu Zhou, Pfaltz et al.
up to 87% *ee*
Reference **105**

L81-Cu Seebach et al.
up to 84% *ee*
Reference **106**

L82 Braga et al.
up to 85% *ee*
Reference **107**

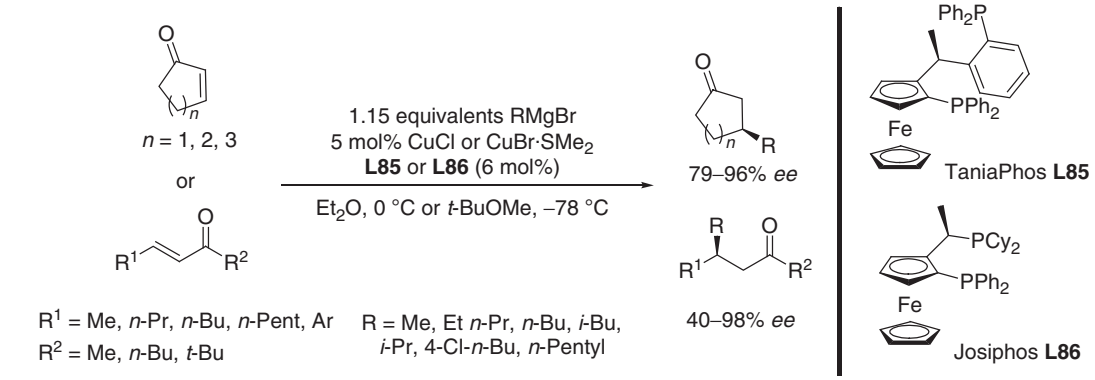
L83 Tomioka et al.
up to 92% *ee*
Reference **108**

L84 Stangeland et al.
up to 92% *ee*
Reference **109**

Figure 18 Selected copper complexes and ligands involved in the development of copper-catalyzed ACA with Grignard reagents.

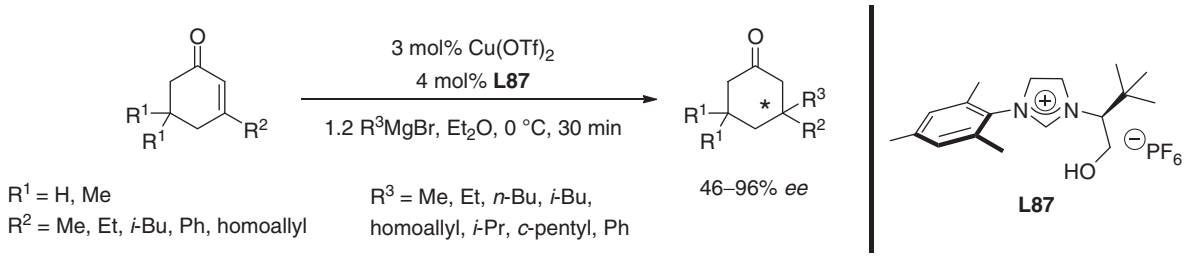
In 2004, Feringa et al. described a successful catalytic system employing ferrocenyl diphosphine ligands, namely Taniaphos **L85** and Josiphos **L86**,[110] able to prevent noncatalyzed Grignard addition and free copper ion-promoted nonstereoselective catalysis.[111] High enantioselectivities were disclosed for the addition of linear alkyl Grignard reagents to a wide range of both cyclic

(up to 96% *ee*) and linear enones (up to 98% *ee*).[112] However, the conjugated addition of the secondary alkyl Grignard '*i*PrMgX' provided only moderate enantioselectivity (up to 54%). Nevertheless, recent results obtained with monodentate phosphorus-type ligands such as phosphoramidite[113] or SimplePhos[114] did not provide higher enantiocontrol than with **L85** and **L86** (Scheme 9).



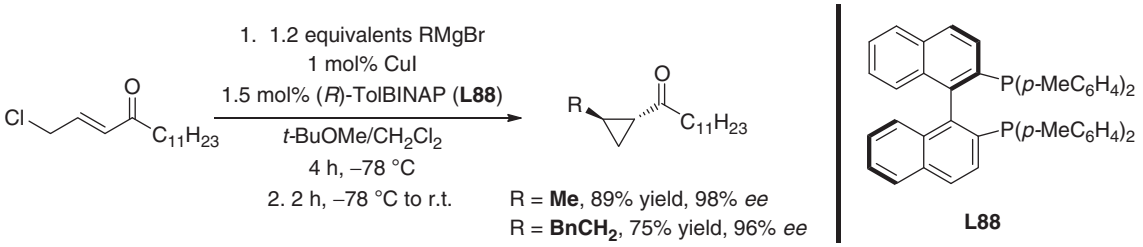
Scheme 9 Copper/ferrocenyl-diphosphine-catalyzed efficient conjugated addition with cyclic and acyclic enone.

The efficient creation of all carbon quaternary stereogenic centers constitutes an important challenge in organic synthesis. In 2006, Alexakis, Mauduit and coworkers introduced NHC as chiral ligands for copper-catalyzed conjugated addition of Grignard reagents to a variety of β,β'-disubstituted enones.[115] The combination of Cu(II) triflate and bifunctional alkoxy-NHC ligand **L87** derived from *t*-leucinol offered good to excellent *ee*s (up to 98%) (Scheme 10). The same groups recently demonstrated the possibility to scale up this robust and efficient methodology.[116]



Scheme 10 Copper/NHC-catalyzed all carbon quaternary stereogenic centers.

In 2010, Feringa and coworkers described an interesting application of the ACA of Grignard reagents to 4-chlorocrotonates using the readily available TolBINAP ligand **L88** (Scheme 11). The tandem CA-intramolecular enolate trapping offered access to *trans*-1,2-disubstituted cyclopropanes with excellent enantioselectivities (up to 98% *ee* with 4-chloro-substituted α,β-unsaturated ketones).[117]

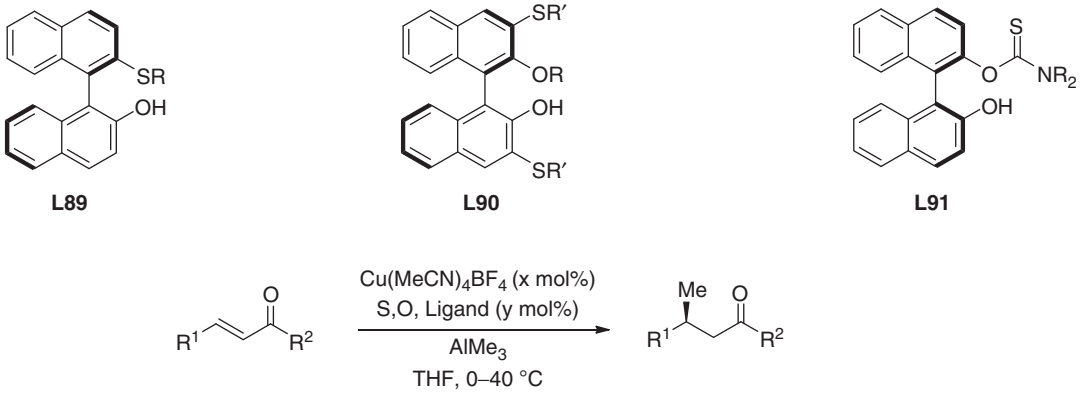


Scheme 11 Copper-catalyzed tandem conjugated addition with Grignard reagents – intermolecular enolate trapping.

4.04.2.1.1.3 Organoaluminum reagents

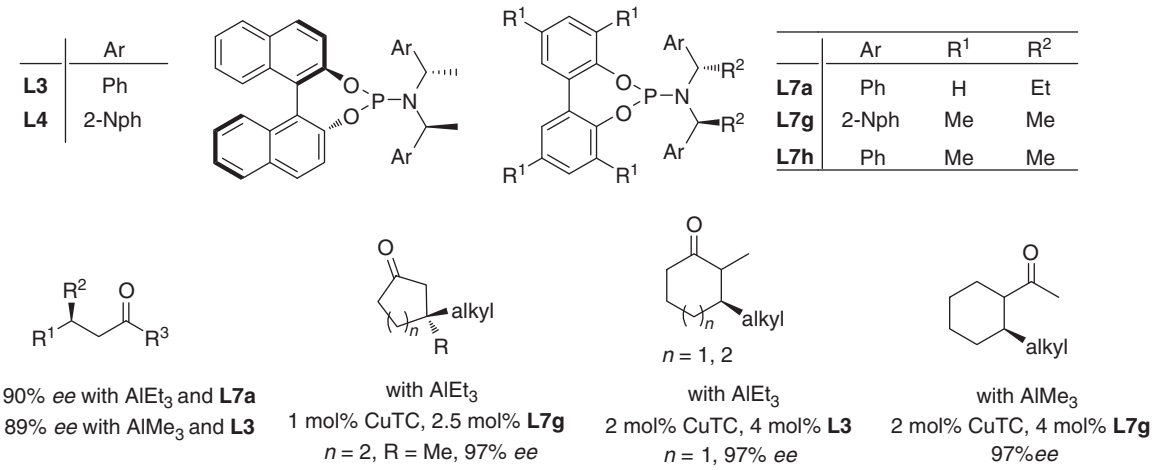
Organoaluminum reagents represent an important class of organometallic nucleophiles in copper-catalyzed ACA. In fact, trialkylaluminums constitute an interesting alternative to organozinc reagents, thanks to their readily availability and modular preparation. Early reports referring to the use of organoaluminum reagents for copper-catalyzed ACA were reported by Woodward

and coworkers (Scheme 12).[118] This extensive study on heterodonor S,O ligands, particularly a binaphthol-based family **L89–91**, demonstrated the potential of trialkylaluminum to provide the desired addition products with good to high regio- and enantioselectivity (up to 93% *ee* with disubstituted linear enones).



Scheme 12 Heterodonor S,O ligands in copper-catalyzed ACA with organoaluminum.

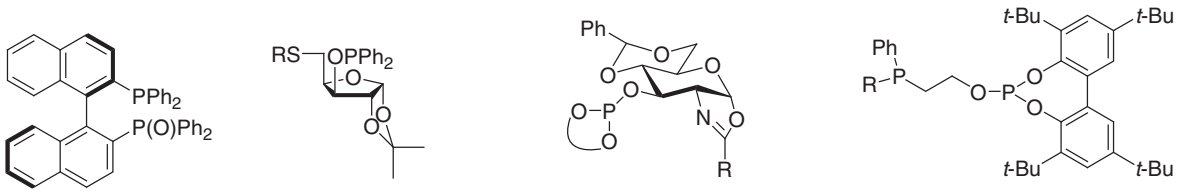
Soon after, the phosphoramidite ligand family demonstrated large efficiency in the copper-catalyzed ACA of organoaluminum reagents (Scheme 13). High selectivities were obtained for the addition of $AlMe_3$ and $AlEt_3$ to cyclohexenone, cycloheptenone, and disubstituted linear enones.[119] Interestingly, organoaluminum reagents display enhanced reactivity toward challenging substrates such as sterically hindered β,β-disubstituted enones. Accordingly, Alexakis and coworkers described efficient strategies to construct all-carbon stereogenic quaternary centers from β -substituted cyclic enones.[120] Recently, Zhang and coworkers reported new types of biphenyl phosphoramidite ligands (**L11**) containing a D_2-symmetric backbone, which afforded up to 93% *ee* for the conjugated addition of $AlEt_3$ with chalcone.[121]



Scheme 13 Phosphoramidite ligands in copper-catalyzed ACA with organoaluminums.

Numerous different phosphine-based ligands were also evaluated in the copper-catalyzed conjugate addition of organoaluminum with inconstant satisfaction. Binaphthol-based diphosphite ligands were applied with success for the addition of $AlMe_3$ to cyclic enones (up to 96% with cyclohexenone).[119c,122] However, only moderate selectivities were observed with binaphthol-monophosphite ligands,[123] and with mixed donor ligands such as P,O;[124] P,N;[125] P,S;[75] and P,P′.[126] An exception is the heterobidentate chiral Binapo ligand that gave good to high enantioselectivities (up to 91% *ee*) in the conjugated methyl- and ethyl-addition to cyclic and acyclic enones (Figure 19).[127]

Recently, Endo et al. developed multinuclear complexes based on new mixed P,OH ligands for the ACA of trialkylaluminum reagents to acyclic enones. With ligands **L31**, **L32**, and **L33**, extremely high yields and enantioselectivities were obtained for the



L92: Binapo

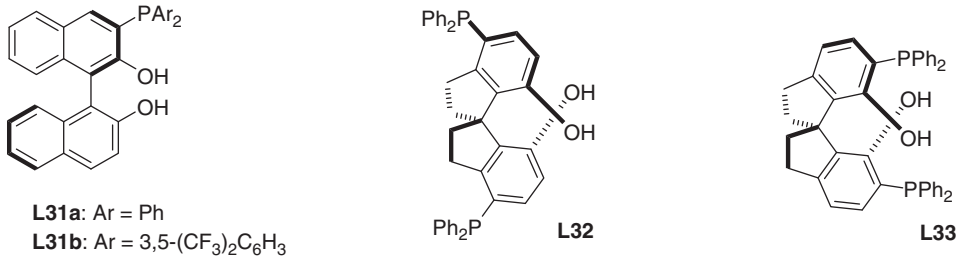
L93: Thioether-phosphinite

L54: Sugar-phosphite-oxazoline

L94: Phosphino-phosphite

Figure 19 Typical examples of phosphine-based ligands evaluated in ACA with organoaluminum reagents.

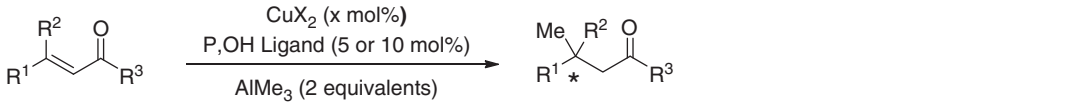
conjugated addition of trimethylaluminum to acyclic enones for the construction of both tertiary and quaternary carbon centers (Scheme 14).



L31a: Ar = Ph
L31b: Ar = 3,5-$(CF_3)_2C_6H_3$

L32

L33



R^1 = Ar, alkyl
R^2 = H, Ar, alkyl
R^3 = Ar, alkyl

R^2 = H: up to 98% yield and 98% *ee* with **L31b** or **L32**
R^2 = Ar, Alkyl: up to >98% yield and >98% *ee* with **L32** and **L33**

Scheme 14 $AlMe_3$ addition to acyclic enones for the construction of all carbon quaternary centers.

The copper-catalyzed enantioselective conjugated addition of alkenylalane nucleophiles has attracted attention during the last decade. Phosphoramidites,[120b] ferrocenyl-based phosphonites **L95**,[128] and recently, phosphinamine **L60**[129] ligands were evaluated in this process. Alexakis and coworkers demonstrated that phosphinamine ligands offered high enantioselectivities for the construction of all carbon quaternary centers from conjugated addition of both alkyl- (up to >98% *ee*)[129a] and alkenylalanes (up to 89% *ee*)[129b] with β-substituted cyclic enones (Scheme 15).

Diaminocarbene ligands offered important improvements for the conjugated addition with β-substituted cyclic enones, particularly with challenging β-substituted cyclopentenones. Hoveyda and coworkers successfully applied sulfonate- and aryloxide-containing NHC silver complexes for the copper-catalyzed quaternary center constructions with trialkylaluminum reagents and a broad range of nonactivated β-substituted cyclic enones (Scheme 16).[130]

4.04.2.1.1.4 Miscellaneous C-nucleophiles

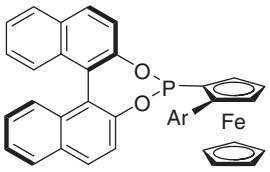
A Cu-catalyzed enantioselective-conjugated addition process involving aryl- and vinyltrifluorosilanes was developed. The transformation can be performed with five-, six-, seven-, and eight-membered ring cyclic enones. Organosilanes are considered less moisture- and oxygen-sensitive than Mg, Zn, Al-based nucleophiles (Scheme 17).[131]

Fletcher and coworkers described the direct use of alkylzirconium, generated *in situ* by hydrometallation of alkenes, as nucleophiles in enantioselective copper-catalyzed conjugated addition to cyclic enones.[132] The robustness of the Schwartz reagent offered large modularity and functional group tolerance in comparison with traditional organometallics (Scheme 18).

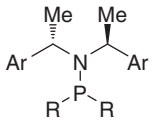
4.04.2.1.2 Addition of hetero-nucleophiles

4.04.2.1.2.1 Conjugate boration

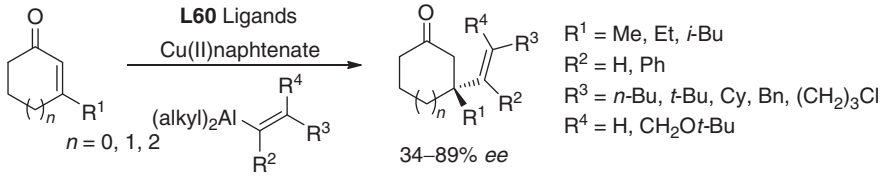
Organoboranes were recently introduced as a nucleophilic source for ECA to α,β-unsaturated carbonyl compounds. The early report, catalyzed by copper, described the enantioselective β-boration of α,β-unsaturated esters and nitriles by a nonracemic copper



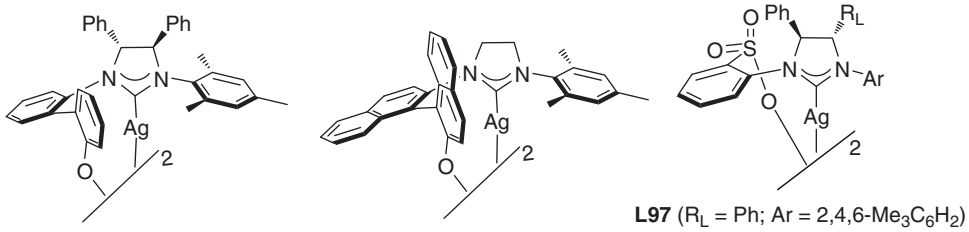
Ferrocenyl-based phosphonites (**L95**):
85% *ee* with Ar = Ph,
$R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Ph$



Phosphinamine ligands (**L60**):
R = alkyl, Ph, 3,5-dimethylbenzene
Ar = Ph, 2-naphthyl

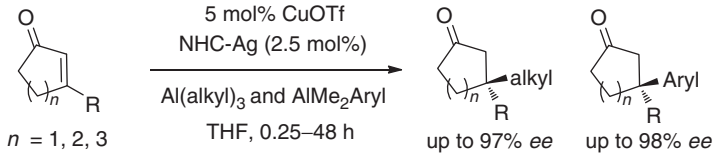


Scheme 15 Copper-catalyzed ACA of alkenylalanes.



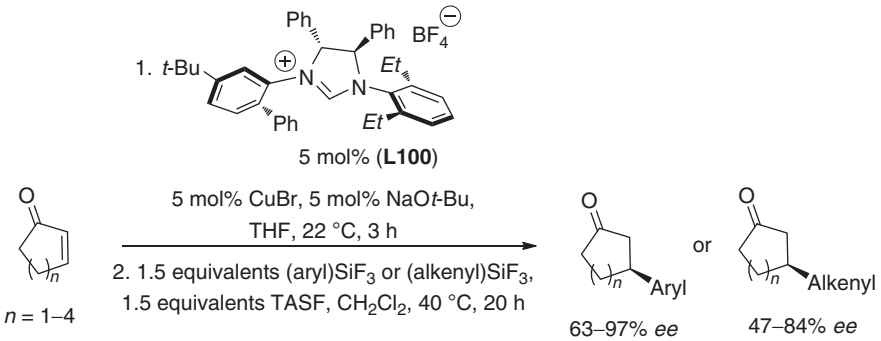
L24 **L96**

L97 (R_L = Ph; Ar = 2,4,6-$Me_3C_6H_2$)
L98 (R_L = H; Ar = 2,4,6-$Me_3C_6H_2$)
L99 (R_L = H; Ar = 2,6-$Et_2C_6H_3$)

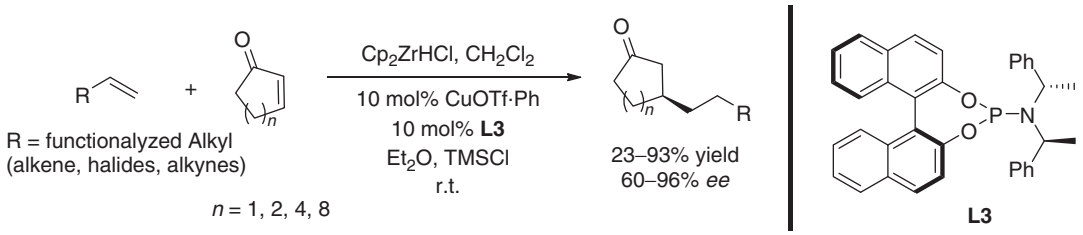


With **L24**: $n = 1$, Aryl = oMeC_6H_4, R = Me, 85% yield, 98% *ee*
With **L98**: $n = 1$, alkyl = Ethyl, R = Me, 97% yield, 97% *ee*
With **L97**: $n = 2$, Alkyl = Ethyl, R = CO_2Me, 91% yield, 83% *ee*
With **L99**: $n = 3$, Alkyl = Ethyl, R = *n*-Bu, 87% yield, 89% *ee*

Scheme 16 Bidentate NHC/copper-catalyzed ACA with non activated β-substituted cyclic enones.

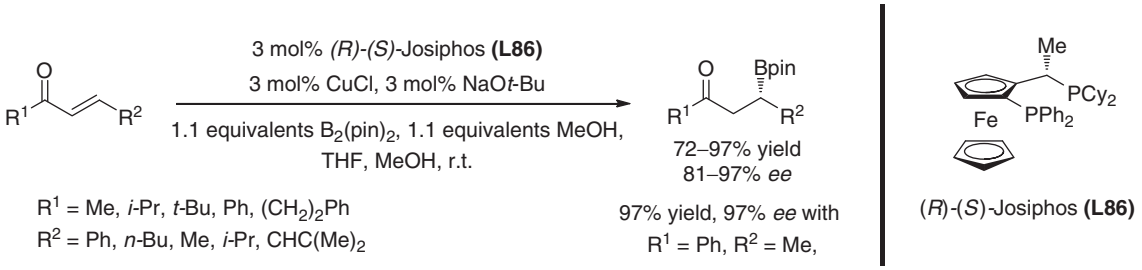


Scheme 17 Cu-catalyzed conjugated addition with aryl- and alkenylsilylfluorides.



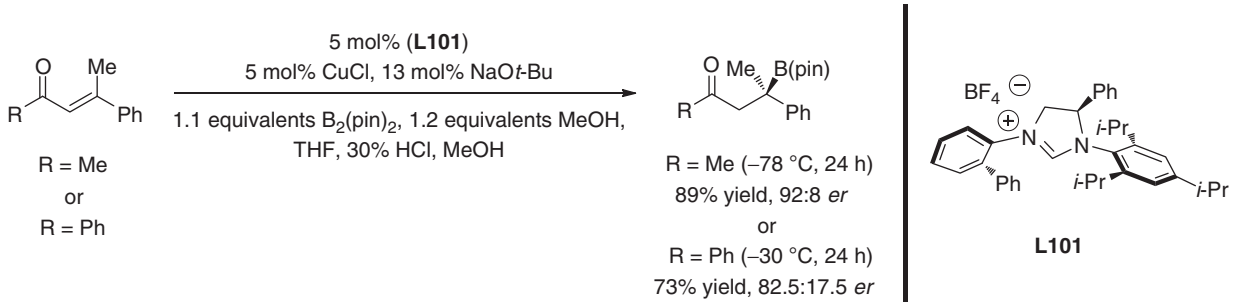
Scheme 18 Cu-catalyzed conjugated addition with alkylzirconium.

phosphine complex with bis(pinacolato)diboron (B_2pin_2).[133] In 2009, Yun and coworkers reported the challenging copper-catalyzed enantioselective addition of B_2pin_2 to acyclic enones. Under mild reaction conditions with alcohol additive and Josiphos or Mandyphos-type ligands, high enantioselecectivity was achieved (Scheme 19).[134]



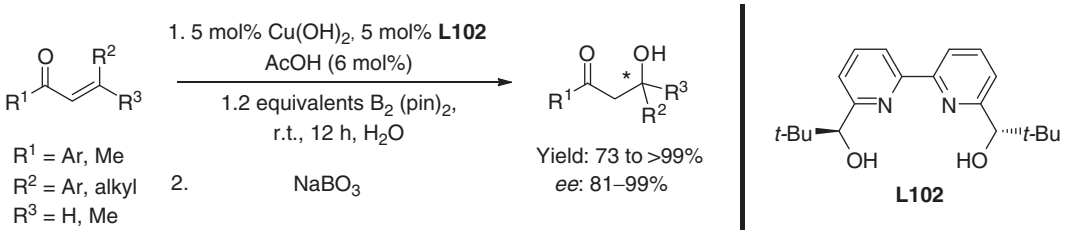
Scheme 19 Copper-catalyzed enantioselective conjugate addition of diboron reagents.

Later, NHCs were employed as chiral ligands in the copper-catalyzed enantioselective boronate addition to electron-deficient alkenes.[135] C_1-symmetric NHC ligand **L101** provided high selectivity to form the desired asymmetric quaternary carbons from trisubstituted acyclic α,β-unsaturated ketones (Scheme 20).[136]



Scheme 20 Copper-catalyzed enantioselective conjugate addition of diboron reagents.

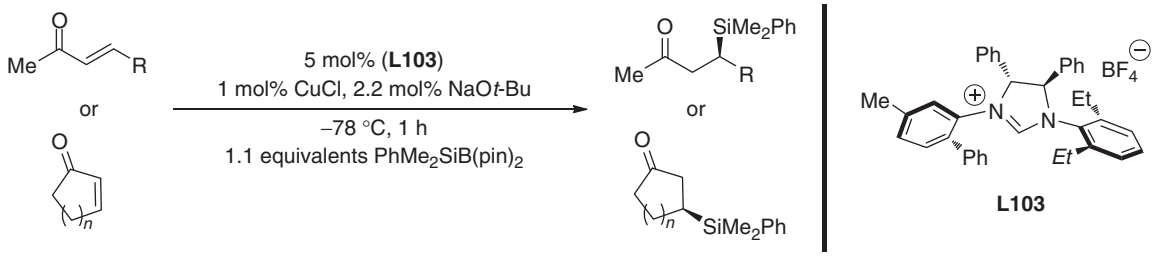
Recently, Kobayashi et al. reported enantioselective boron conjugate addition to various α,β-unsaturated ketones in water (Scheme 21).[137] Excellent yields and enantiomeric excesses were obtained in the presence of the catalytic system $Cu(OH)_2$/**L102** with acyclic enone substrates (up to >99% yield and up to 99% *ee*). Moreover, the methodology appeared highly efficient for the synthesis of optically active tertiary alcohols (two examples: 93% and 97% *ee*).



Scheme 21 Highly enantioselective conjugate addition of diboron reagents in water.

4.04.2.1.2.2 Conjugate silylation

An efficient method for the catalytic enantioselective synthesis of β-silylcarbonyl compounds via C–Si bond formation employed (dimethylphenylsilyl)pinacolatoboron as nucleophile. The copper/NHC system catalyzed silyl conjugated addition to cyclic and acyclic enones with high yield and enantioselectivity (Scheme 22).[138]



R =	Yield (%)	*er*
Me	88	97:3
n-Pent	96	98:2
i-Pr	87	97:3
Ph	91	98.5:1.5
p-$OMeC_6H_4$	94	97:3
p-$CF_3C_6H_4$	97	96:4
o-MeC_6H_4	96	93.5:6.5

	Yield (%)	*er*
n = 1	87	90:10
n = 2	92	97.5:2.5
n = 3	95	97:3
n = 4	95	98:2
n = 1	89	99:1
n = 2	94	99:1
	95	92:8

Scheme 22 Copper-catalyzed enantioselective conjugate addition of silylboron reagents.

4.04.2.2 Esters/lactones/thioesters Substrates

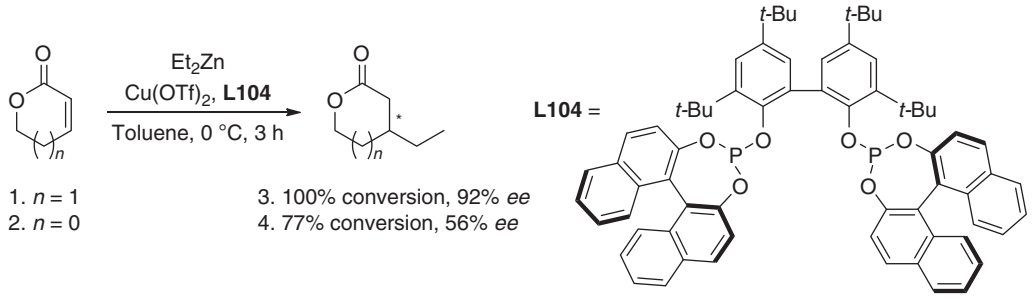
Although unsaturated ketones, either cyclic or acyclic, are the Michael acceptors of choice to perform ECAs and thus evaluate the performances of new chiral ligands to promote asymmetric induction, other substrates have been more sporadically investigated. A number of studies have involved copper-catalyzed ACA of nitroalkenes (see Section 4.04.2.3) but little attention has been devoted to cyclic or acyclic unsaturated carboxylic esters and (thio-) derivatives. This shape contrast can be explained by reactivity issues. Indeed, these Michael acceptors are often less reactive than α,β-unsaturated ketones, and so require either more competent catalysts or more active nucleophiles which are not always compatible with substrates, metals, or ligands. Nevertheless, several ways and catalytic systems have been found to tackle these problems as a function of the nucleophile employed.

4.04.2.2.1 Addition of C-nucleophiles

4.04.2.2.1.1 Organozinc reagents

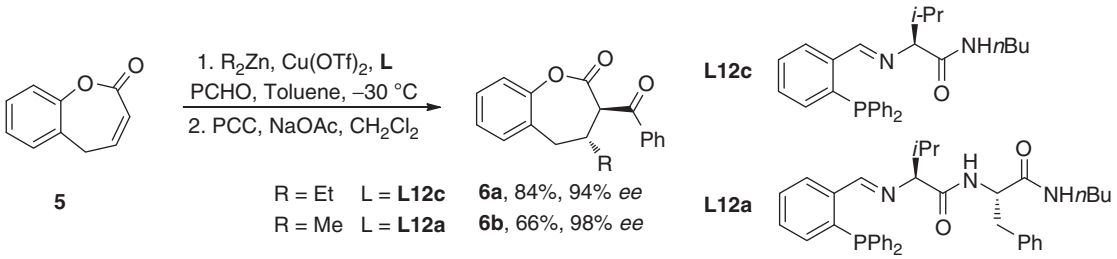
In 2000, Chan and coworkers were the first to disclose the copper-promoted enantioselective addition of organozinc reagents to α,β-unsaturated lactones.[139a] They scrutinized a series of chiral BINAP-based phosphites for the copper(II) triflate-promoted addition of diethylzinc to 5,6-dihydro-2*H*-pyrane **1** (Scheme 23). Although triphenyl- or triethylphosphites gave **3** in only low yields, BINOL-based phosphites were found particularly efficient, up to quantitative conversions. Moreover a good chiral induction was observed with all these ligands, up to 92% *ee* with **L104**. Nevertheless, the enantioselectivity excess dropped significantly when the 5*H*-furan-2one **2** was used as Michael acceptor. Later these results were improved by the use of new chiral diphosphite ligands derived from the H_8-binaphtol giving rise to 98% *ee* for **1**.[139b] The optimization of the reaction conditions, replacement of toluene by diethyl ether, and carrying out the reaction at lower temperature, allowed also to increase the enantioselectivity notably for 5*H*-furan-2one **2**.[139c] Reetz obtained as well good results with similar ligands combining the BINOL moiety and a ferrocene unit.[140] Chiral NHCs were also described to provide an interesting stereocontrol.[141]

Probably the best results for Cu-catalyzed conjugate addition of dialkylzinc reagents to α,β-unsaturated lactones were reported by Hoveyda using amino acid-based phosphanes **L12c** and **L12a** as ligands.[142] Besides reaching respectively 98% and 97% *ee* for



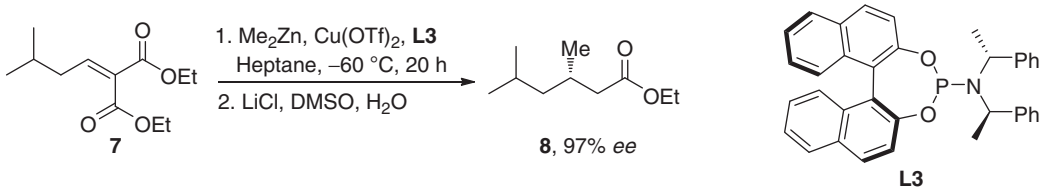
Scheme 23 ACA of diethylzinc to lactones using BINOL-based phosphites as chiral ligands.

the addition of Et_2Zn to lactones **1** and **2**, the catalytic system showed a good efficiency with oxepinone **5** even when the less reactive dimethylzinc was employed (Scheme 24). Of note, to get high yields, reactions were run in the presence of benzaldehyde; probably to prevent ketene formation or an intermolecular Michael addition. The resulting aldol adduct was oxidized into the corresponding diketone **6** which can be subjected to a retro-aldol process to afford the optically enriched alkyl carbonyl compounds. This methodology was successfully applied to other Michael acceptors such as furanones or pyranones.



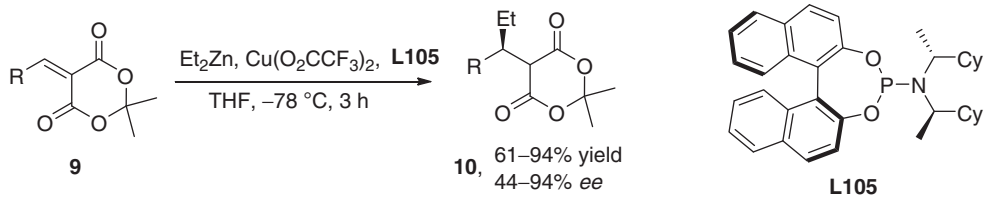
Scheme 24 Enantioselective Cu-mediated addition of dialkylzinc to lactones with amino acid-based phosphanes as chiral ligands.

Simple acyclic α,β-unsaturated esters are not reactive in the 1,4-addition of organozinc reagents, therefore Feringa explored substrates bearing an extra activating group such as nitro or ester.[143] As expected, acyclic α,β-unsaturated nitroacetates are good substrates for the addition of diethylzinc; however, with the phosporamidite **L3** low diastereo- and enantioselectivity were achieved.[185] Suspecting an unfavorable orientation of the nitro group, cyclic analogs such as 3-nitrocoumarin were tested and gave rise to a good chiral induction up to 92% *ee*. As depicted in Scheme 25, the addition of dimethylzinc to unsaturated malonates such as diethyl isopentylidene malonate **7** can be performed with an excellent stereocontrol using the chiral ligand **L3**.[143] After decarboxyaltion, the product **8** was isolated with an *ee* of 97%. Interestingly the methodology can be applied iteratively to construct either *syn*- or *anti*- 3,5-dimethyl carbonyl compounds.

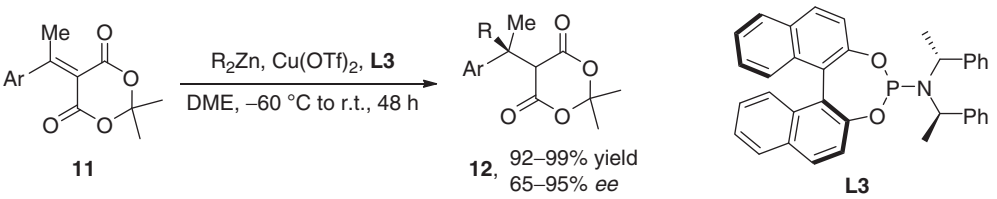


Scheme 25 Copper-catalyzed ACA of dimethylzinc to unsaturated malonates.

In the same time, Carreira and coworkers investigated analogous cyclic substrates **9** that can be synthesized straightforwardly by a condensation between aldehydes and Meldrum's acid (Scheme 26).[144] With these acceptors, it was possible to reach high enantiomeric excess for the addition of diethylzinc mediated by a copper(II) trifluoroacetate/chiral phosphoramidite **L105** catalytic system. Later, Fillion examined 5-(1-arylmethylidene) Meldrum's acids **11** to form all-carbon benzylic quaternary stereocenter (Scheme 27).[145] Once again, chiral phosphoramidites proved to be excellent ligands and highly enantioselective addition of dialkylzinc reagents was achieved. This reaction was found broad in scope except *ortho*-substituted aryl groups which are not tolerated and its synthetic potential was demonstrated by the preparation of succinimides, γ-butyrolactones, and β-amino acids derived from Meldrum's acid. This work was extended to 5-(3-aryl-2-propenylidene) Meldrum's acids to carry out 1,6-conjugate addition with less success because only 65% *ee* was reached.[146]

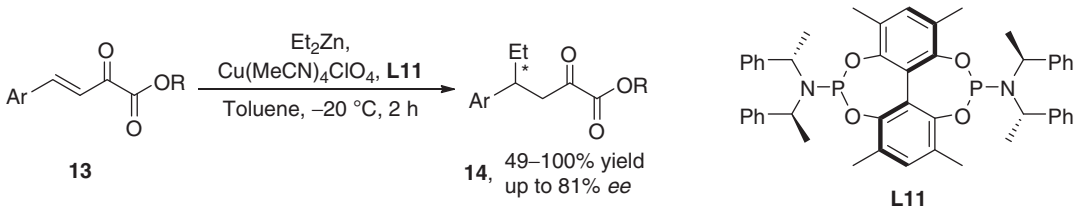


Scheme 26 Copper-catalyzed ACA of dialkylzinc to 5-(1-arylmethylidene) Meldrum's acids.



Scheme 27 Copper-catalyzed ACA of dialkylzinc to 5-(1-arylethylidene) Meldrum's acids.

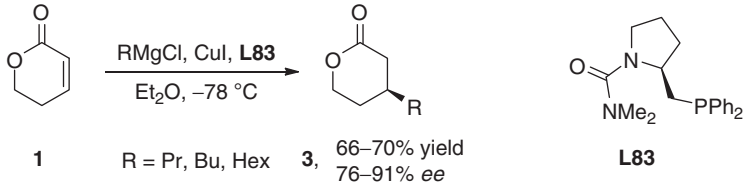
As depicted in Scheme 28, other Michael acceptors, β,γ-unsaturated α-keto esters, are suitable substrates for the conjugate addition of diethylzinc.[147] After an optimization step, Zhang and coworkers identified a copper(I) salt, $Cu(MeCN)_4ClO_4$ as the best metal precursor for both activity and enantioselectivity. Ligand screening revealed that chiral phosphoramidites are competent, in particular those structurally advanced, for instance **L11** including a D_2-symmetric biphenyl moiety. Reaction scope in respect of β,γ-unsaturated α-keto esters **13** was found broad and surprisingly the nature of the R group plays an important role in chiral induction; the configuration was reversed when a methyl was replaced by a benzyl. Sterically hindered aryl group at the γ-position led to decrease the enantiomeric excess. Recently, Alexakis reported that Me_2Zn can be added to α-keto esters with high stereocontrol but low yield (93% *ee*, 14% yield) using (*R*)-BINAP.[148]



Scheme 28 Copper-catalyzed ACA of diethylzinc to β,γ-unsaturated α-keto esters.

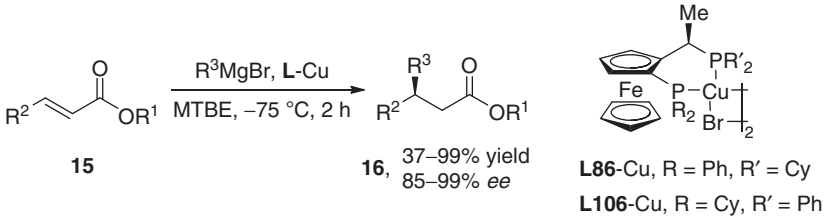
4.04.2.2.1.2 Organomagnesium reagents

In comparison with dialkylzinc, alkylmagnesium reagents are more valuable nucleophiles because of their better reactivity, their higher molecular diversity, their easy preparation, and commercial availability.[100] However, these reagents are not compatible with phosphoramidites which are extensively used in ACA. Therefore, other enantioselective ligands were developed. To the best of our knowledge, Tomioka was the first to disclose the utilization of organomagnesium chlorides to Cu-promoted enantioselective 1,4-addition to lactones.[149] Using a proline-based phosphine containing an urea function **L83**, the expected products **3** were isolated in moderate yields and good enantiomeric excesses, especially with butyl- and hexylmagnesium chlorides, 91% and 90% *ee*, respectively (Scheme 29). Similar results were obtained for the addition of ethylmagnesium bromide to **1** mediated a copper(I) salt in association with chiral ferrocenyl-based diphosphines such as Taniaphos or Josiphos,[150] or TADDOL-based phosphites.[151]



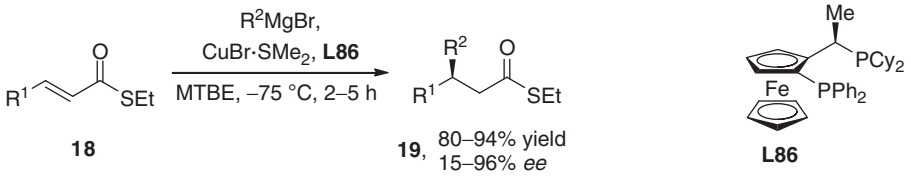
Scheme 29 Enantioselective conjugate addition of RMgCl to α,β-unsaturated lactone **1**.

Feringa and coworkers focused their efforts on the development of a catalytic system efficient for acyclic α,β-unsaturated esters as Michael acceptors.[152] Having obtained successful results with chiral ferrocenyl-based diphosphines,[150] they explored the potential of these ligands to the enantioselective addition of Grignard reagents to α,β-unsaturated esters **15** (Scheme 30).



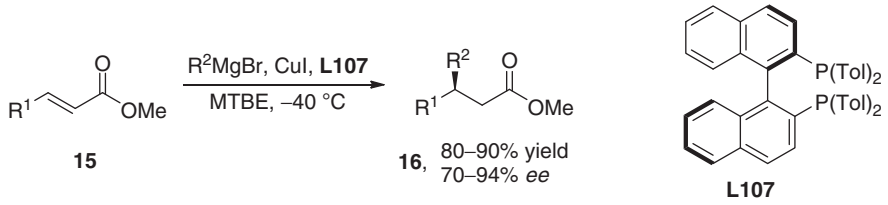
Scheme 30 Cu-mediated ACA of RMgCl to acyclic α,β-unsaturated esters.

At preliminary study, it was noticed that the nature of the ester (R^1) impacted significantly the reaction stereocontrol; the bulk increase led to reduced enantiomeric excesses. Interestingly, complexes **L86**-Cu and **L106**-Cu, which were easily prepared, proved to be air-stable and improved the procedure simplicity, were found particularly efficient. Of note, this is one of the rare examples of the utilization of well-defined complexes in Cu-catalyzed ACA. The reaction scope was found really broad with at least 20 examples and was enlarged to unsaturated thioesters **18** with an *in situ*-generated catalytic system including (*R*,*S*)-Josiphos **L86** and CuBr·SMe_2 (Scheme 31).[153] High chiral induction was observed except with branched-chain Grignard reagents. This methodology was applied to asymmetric total syntheses of mycocerosic and phthioceranic acids, and (−)-lardolure using iterative Cu-catalyzed ACAs as key steps. Recently, coumarins as Michael acceptors were examined giving rise to addition products with excellent enantioselectivities.[154]



Scheme 31 Cu-promoted enantioselective addition of RMgCl to α,β-unsaturated thioesters.

To accomplish the copper-catalyzed ACA of alkylmagnesium bromides to α,β-unsaturated esters, Ji and Loh also investigated diphosphines, but with a chirality lying of the binaphtyl moiety, for instance Tol-BINAP **L107**.[155] Optimized reaction conditions were found alike those reported for ferrocenyl-based diphosphines with a copper(I) salt and *tert*-butylmethyl ether as solvent (Scheme 32). Products **16** were isolated with excellent stereocontrol (superior to 90% *ee*) and this catalytic system tolerates better Grignard reagents substitutions, even with thioesters as Michael acceptors.[153d] As a proof of efficiency, several syntheses of natural products were achieved using CuI/Tol-BINAP-catalyzed conjugate addition as key step[156] or advanced substrates were successfully tested.[157]

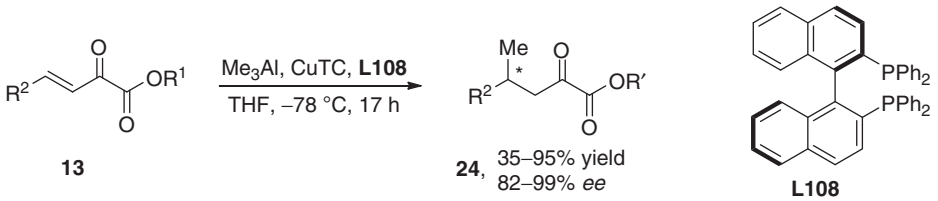


Scheme 32 Cu-mediated ACA of RMgCl to α,β-unsaturated esters with BINAP-type ligand.

4.04.2.2.1.3 Organoaluminum reagents

The problem of ECA to β,γ-unsaturated α-keto esters **13** could not be acceptably addressed with organozinc reagents (either low yield and high enantioselectivity or good yields but *ee* up to 81%)[147] or Grignard reagents (only 1,2-addition occurs)[148] and therefore, organoaluminum reagents were investigated as nucleophiles. Chan already demonstrated that trimethylaluminum reacted with α,β-unsaturated lactone **1** to give the expected addition product with a moderate conversion (72%) and promising stereocontrol (81% *ee*).[71] Recently, Alexakis reported the highly ECA of trimethylaluminum to ketoesters **13** using copper(I)

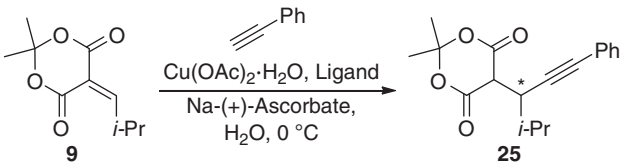
thiophene-2-carboxylate (CuTC) and (*R*)-BINAP **L108** (Scheme 33).[148] Even if the reaction scope was not examined with respect to the aluminum nucleophile, this reaction showed a good tolerance to variously substituted ketoesters **13**; steric hindrance of R^2 did not affect stereocontrol.



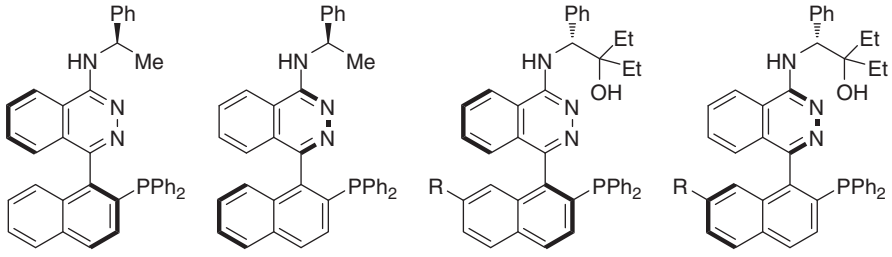
Scheme 33 Cu-promoted 1,4-conjugate addition of trimethylaluminum to β,γ-unsaturated α-ketoesters.

4.04.2.2.1.4 Miscellaneous C-nucleophiles

In addition to the well-known dialkylzinc, alkylmagnesium halides or trialkylaluminum reagents, several studies demonstrated that other carbon nucleophiles could be used. After having showed that terminal alkynes could be added to Meldrum's acid-derived acceptors using a copper-mediated catalysis,[158] Carreira tackled the development of an enantioselective version.[159] At first, a variety of chiral ligands were screened before focusing on PINAP ligands, which are analogs of QUINAP incorporing a phtalazine moiety (Scheme 34). Using ligand **L109**, the addition product **25** was obtained with good optical purity (80% *ee*, entry 1); however, its diastereomer **L110** furnished **25** in 37% *ee*. These results highlighted a strong matched/mismatched effect and led to testing atropodiastereomer combinations before identifying **L114** as the most efficient (entry 6). The reaction scope with respect to the Meldrum's acid derivative substituents showed that phenylacetylene could be added with *ee* spaning from 82% to 95% and good yields.

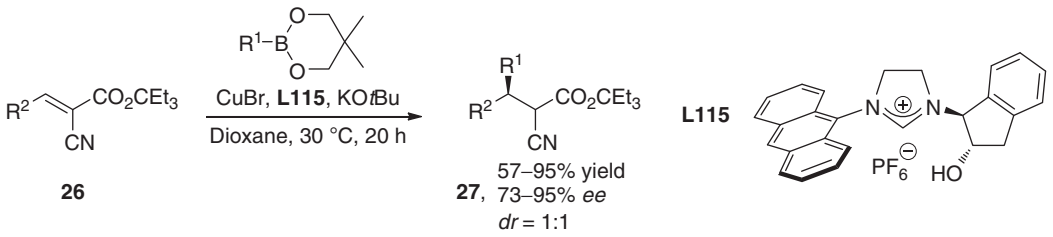


Entry	Ligand	Temperature (h)	Conversion (%)	*ee* (%)
1	**L109**	18	58	80 (*S*)
2	**L110**	20	33	37 (*R*)
3	**L111**	14	49	48 (*S*)
4	**L112**	14	44	8 (*S*)
5	**L113**	11	40	94 (*R*)
6	**L114**	11	100	95 (*R*)



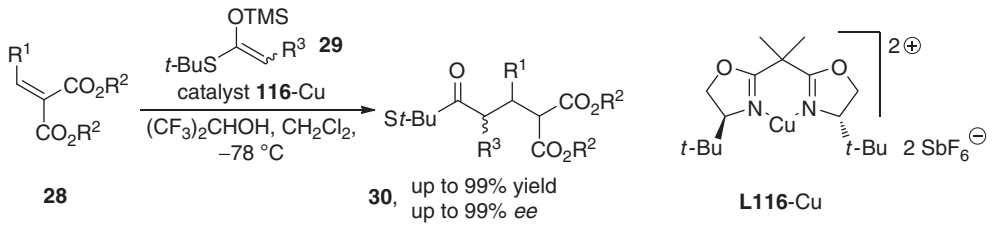
Scheme 34 Cu-catalyzed 1,4-conjugate alkyne addition.

Whereas organoboronic acids are now widely used in organic synthesis, until recently these mild nucleophiles were never used in asymmetric copper-promoted 1,4-conjugate addition. Shintani and Hayashi disclosed that to carry out this addition the carbon–carbon double bond must be substituted by two electron-withdrawing groups, either esters or nitriles, or even better one ester and one nitrile.[160] After an optimization process, it was found that copper(I) bromide in association with an *in situ*-generated NHC bearing an alkoxy group from the salt **L115** performed well for the asymmetric addition of organoboronates to alkylidene cyanoacetates **26** (Scheme 35). Yields are good (>80%) except when R^2 is an *ortho*-substituted aryl as well as the stereocontrol (87–95% *ee*) with the exception of alkylboronates.



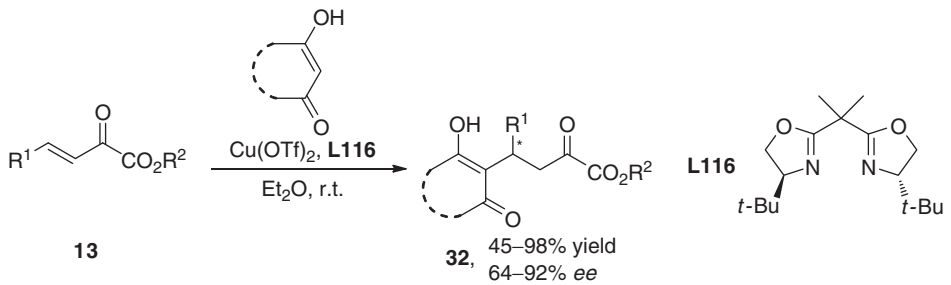
Scheme 35 Enantioselective Cu-promoted 1,4-conjugate organoboronate addition to electron-deficient C–C double bonds.

Nowadays, Michael addition is a well-known and used transformation allowing the construction of quaternary stereocenters by C–C bond-forming reactions (or C–X bond for heteroatom nucleophiles, see Section 4.04.2.2.2) between a nucleophile and an activated alkene partner. This reaction has been extensively investigated since two decades, notably with the development of organocatalysts which are really competent for different types of Michael addition, particularly in enantioselective versions. In addition to organocatalysts, Lewis acids such as copper(II) salts were found capable of promoting this reaction and when they are associated with chiral ligands, in general bis(oxazoline), optically enriched Michael adducts could be obtained. Following early works of Bernardi and Scolastico[161] who reported stoichiometric asymmetric Mukaiyama–Michael additions, Evans and coworkers developed the first catalytic enantioselective addition of enolsilane to α,β-unsaturated esters using C_2-symmetric Cu(II) complexes as chiral Lewis acids.[162] They provided a detailed and comprehensive study of the parameters governing the formation of 3-substituted *tert*-butyl 4,4-dicarbomethoxy-butanethioate **30** as well as its stereocontrol (Scheme 36). Catalyst **L116**-Cu with the *tert*-butyl group attached to oxazoline stereocenter gave the highest enantiomeric excesses and could not be improved afterward.[163] The diastereoselectivity was found to be correlated with enolsilane **29** geometry. Various alkyl-, aryl-, or heteroaryl-substituted malonate derivatives were perfectly tolerated giving excellent enantiomeric excesses. The scope was later broadened to β-enamidomalonates.[164] Evans made interesting studies based on the crystallization of intermediates to explain both diastereo- and enantioselectivities of the nucleophile attack.



Scheme 36 Enantioselective Cu-catalyzed Mukaiyama–Michael reaction of enolsilane **29** and alkylidene malonate **28**.

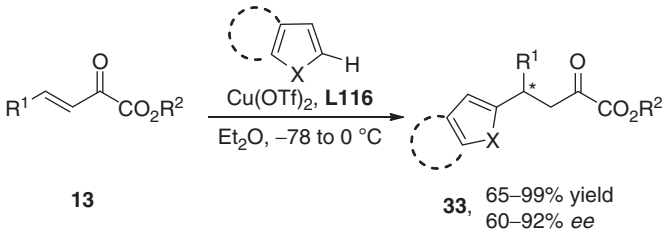
Jørgensen et al. used 1,3-dicarbonyl compounds as nucleophiles to achieve a Michael addition with β,γ-unsaturated α-keto esters **13** in the presence of $Cu(OTf)_2$ and the bis(oxazoline) **L116**.[165] Thus, several adducts **32** of 4-hydroxycoumarins, 4-hydroxy-2-pyrone, or 3-hydroxy-1*H*-phenalene were isolated with moderate to quantitative yields and a good stereoinduction spanning from 63% to 92% *ee* (Scheme 37). Recently, Feng showed that both chemical yield and enantioselectivity could be improved by replacing oxazoline **L19** by a proline-derived *N,N*′-dioxide ligand.[166]



Scheme 37 Asymmetric Michael addition of 1,3-dicarbonyl compounds to β,γ-unsaturated α-keto esters.

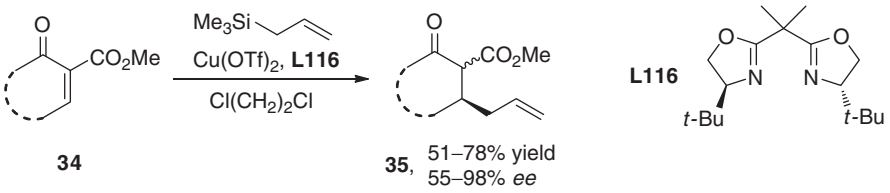
In parallel to Michael addition, Jørgensen investigated asymmetric Cu-catalyzed Friedel–Crafts alkylation with the addition of aromatic and heteroaromatic molecules to activated alkenes such as acyclic unsaturated keto esters **13**.[167] The same catalytic system than for Michael addition was found able to get high enantioselective excess for the addition of indoles, furans, and 1,3-dimethoxybenzene to **13** (Scheme 38). Nevertheless, the enantioselectivity decreased significantly for alkylidene

malonates.[167b] To improve the Friedel–Crafts reaction stereocontrol with alkylidene malonates, Tang built and screened a library of bis(oxazoline) to identify candidates less expensive than the *tert*-butyl oxazoline **L116**.[168] The range of Michael acceptors was successfully widened to ethenetricarboxylates, but the development of its asymmetric intramolecular variant failed.[169]



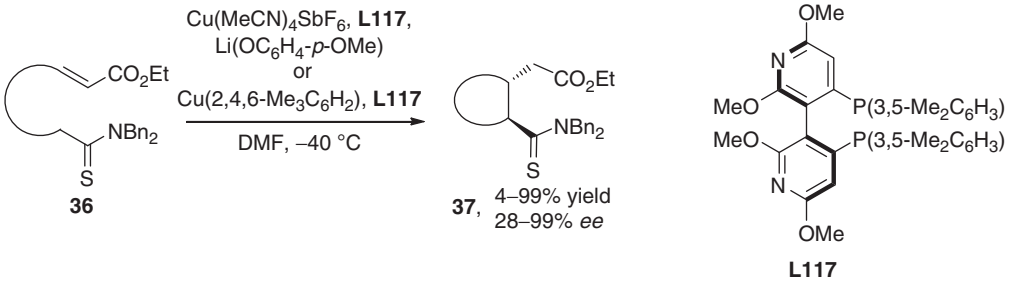
Scheme 38 Enantioselective copper-promoted Friedel–Crafts alkylation of β,γ-unsaturated α-keto esters.

The Hosomi–Sakurai reaction is an addition involving the Lewis acid-promoted allylation of various electrophiles with allyltrimethysilane. In 2008, Snapper and Shizuka reported an enantioselective allylation of cyclic unsaturated keto esters **34** (Scheme 39).[170] After the screening of a large number of oxazoline ligands, it has been shown that **L116** was the most efficient to obtain both high conversion and good enantioselectivities. Five-, six-, and eight-membered cyclic keto esters were tested and allylated products **35** were obtained with moderate to good chiral induction. Sterically demanding substrates required higher reaction temperatures, which has been translated into a selectivity decrease.



Scheme 39 Enantioselective Cu-mediated Hosomi–Sakurai conjugate allylation.

Following their work aimed to develop the utilization of thioamides as pronucleophiles for various additions, Kumagai and Shibasaki were interested in direct catalytic asymmetric intramolecular conjugate addition of thioamides to α,β-unsaturated esters to provide optically enriched five- and six-membered carbocycles.[171] As depicted in Scheme 40, this transformation required a fine-tuned catalytic system composed by a hard Brønsted base and a soft Lewis acid and in association with a chiral ligand **L117** to generate the thioamide enolate. This reaction was found to be somewhat substrate-dependent as stated by the variations observed in chemical yields, diastereoselectivity, and enantioselectivity. Of note, the major cyclic product isolated **37** was always the one with ester and thioamide functions in an *anti* fashion.



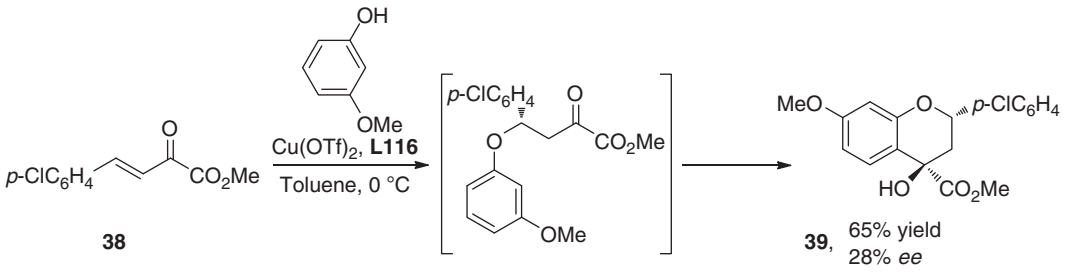
Scheme 40 Direct Cu-promoted asymmetric intramolecular conjugate addition of thioamides.

4.04.2.2.2 Addition of hetero-nucleophiles

4.04.2.2.2.1 Oxa-Michael addition

During the scope investigation of the catalytic system $Cu(OTf)_2$/bis(oxazoline) **L116** in Michael addition, phenols were looked at to perform a tandem oxa-Michael addition – Friedel–Crafts alkylation reactions as strategy for the synthesis of chiral chromanes.[172] Scheme 41 shows the addition of phenol onto the unsaturated keto ester **38** to give an adduct which was directly converted into chromane **39** by a Friedel–Crafts alkylation. Unfortunately, the isolated yield was moderate because of competition

with direct *C*-conjugate addition and the enantiomeric excess disappointing. Higher *ee*s were obtained with $Mg(OTf)_2$ as Lewis acid and screening other bis(oxazolines).[163]

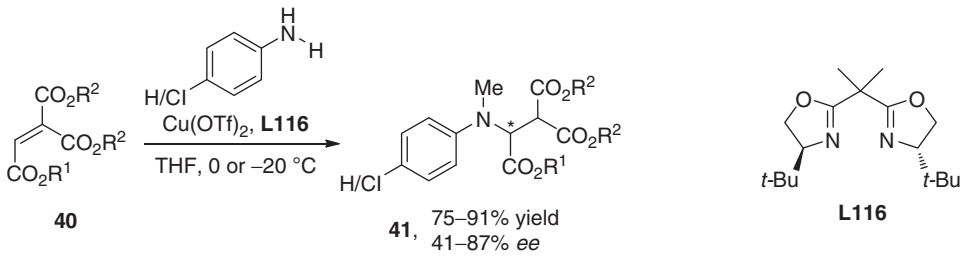


Scheme 41 Oxa-Michael addition catalyzed by copper Lewis acid and chiral bis(oxazoline).

4.04.2.2.2.2 Aza-Michael addition

Hydroxylamine derivatives were early used as nucleophiles in catalytic asymmetric Michael addition to doubly activated substrates, alkylidene malonates, in the presence of the Cu(II)-**L116** complex to give low to moderate *ee*s (up to 29% *ee*).[173] These results were further improved by the use of a bulkier amine as nucleophile, *N*,*O*-bis(trimethylsilyl)hydroxylamine (up to 77% *ee*).

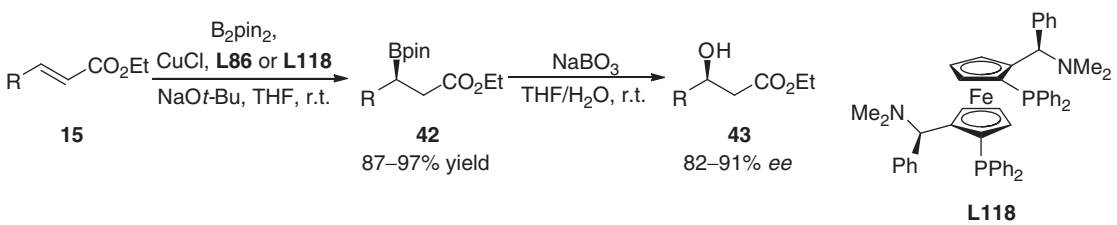
Recently, Yamazaki and coworkers scrutinized another type of *N*-nucleophiles for aza-Michael addition to ethenetricarboxylates.[174] Anilines reacted with ethenetricarboxylates **40** smoothly at room temperature without any catalyst. However, a Lewis acid sped up reaction progress more importantly associated with a chiral ligand such as the bis(oxazoline) **L116** furnished optically enriched adducts **41** (Scheme 42). In spite of good chemical yields, the chiral induction was found fluctuating as a function of the substrate.



Scheme 42 Asymmetric Cu-catalyzed Michael addition of anilines to ethenetricarboxylates.

4.04.2.2.2.3 Conjugate boration

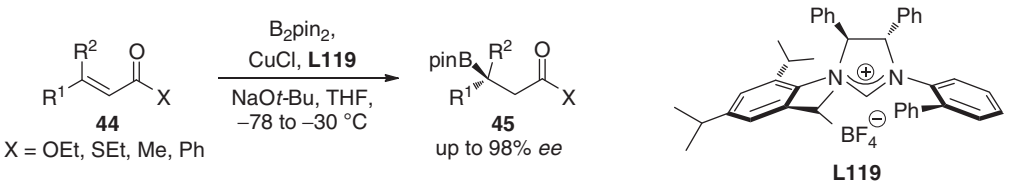
Organoboron compounds are key reagents in organic chemistry enabling many chemical transformations and can be prepared principally by the addition of diboron derivatives to alkenes. Although the enantioselective addition of diboron reagents has been extensively studied with rhodium- or palladium-based catalysts, few examples described the asymmetric copper-catalyzed addition of mainly bis(pinacolato)diboron, B_2pin_2, to electron-deficient alkenes, C–C double-bearing esters or nitrile functions. Yun was the first to demonstrate that *β*-boration of cinnamonitrile could be performed in an enantioselective manner using copper(I) chloride and (*R*,*S*)-Josiphos **L86**.[175a] A more detailed study revealed latter that other chiral ligands provided a good stereocontrol such as ferrocenyl-based ligands **L118** for acyclic *α*,*β*-unsaturated esters (Scheme 43)[175b] or Taniaphos for lactones.[175c] For practical reasons, enantiomeric excesses were determined from hydroxy analogs **43** obtained after oxidation. Guiry and Fernández



Scheme 43 Asymmetric boration of *α*,*β*-unsaturated esters and nitriles mediated by copper.

reported that new axially chiral P-N ligands derived from quinazolinap moiety were successfully applied to the borylation of α,β-unsaturated esters using an identical catalytic system, however with *ee*s values low to correct (up to 79%).[176]

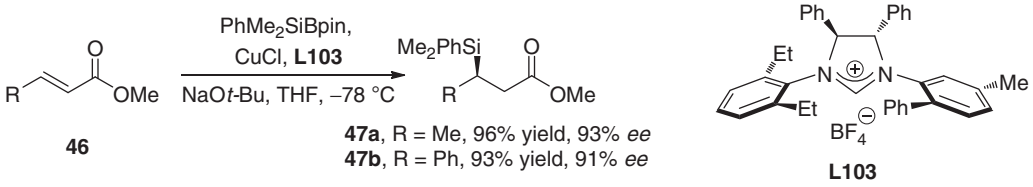
The main drawback of the systems presented above is the inability to catalyze the addition of bis(pinacolato)diboron to trisubstituted alkenes. Therefore, more active catalysts, Cu-based NHC complexes were tested to achieve this transformation.[177] Hoveyda scrutinized various imidazolidinium salts as chiral NHC precursors and identified **L119** allowing to reach high stereoinduction (Scheme 44). Although aryl, alkyl-substituted α,β-unsaturated esters gave excellent yields and high enantiomeric excess values, for dialkyl-substituted analogs, results were found more fluctuating. To solve this problem, thioester equivalent substrates were tested and improved enantioselectivities were observed. Unsaturated ketones were also successfully applied but with a somewhat lower stereoselectivity. In parallel to this study, Yun developed a competent catalyst for β-boration of trisubstituted alkenes using bisphosphine (*S,S*)MeDuphos.[178] Other attempts to achieve boration of α,β-unsaturated esters with different chiral NHCs are reported with more or less success.[179]



Scheme 44 Asymmetric boration of trisubstituted alkenes catalyzed by copper-bearing chiral NHC.

4.04.2.2.2.4 Conjugate silylation

The formation of a carbon stereocenter bearing an Si-group in a catalytic and asymmetric manner is a very challenging research goal that can be addressed either by conjugate-addition of carbon nucleophile to silyl-substituted C–C double bonds or their conjugate reduction. Alternatively, Hoveyda tackled the enantioselective formation of C–Si bonds through the conjugate addition of silyls using Cu-based NHC complexes.[180] After having optimized the catalytic system composed from Cu(I) chloride, **L103** as NHC precursor, and sodium *tert*-butoxide to generate *in situ* the NHC, the reaction scope was investigated including few α,β-unsatured esters (Scheme 45). Lactone **1** gave interesting results, 95% yield and 84% *ee*, but acyclic unsatured esters **46** were found to be better substrates with an excellent stereocontrol of the chiral center.



Scheme 45 Enantioselective silylation of α,β-unsaturated esters.

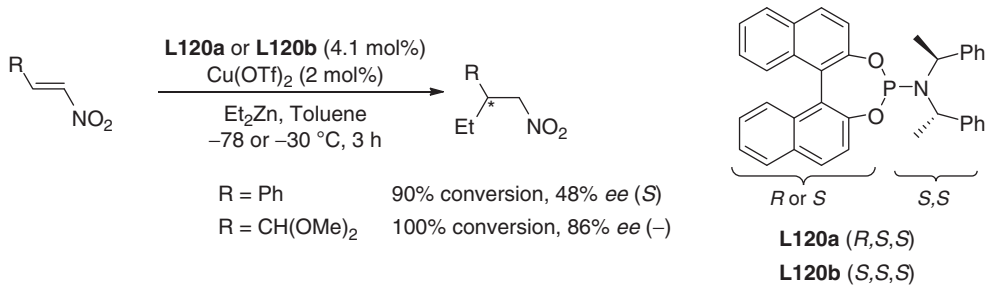
4.04.2.3 Nitroolefins

Among the wide variety of Michael acceptors, nitroolefins are certainly the most useful one for synthetic applications as the nitro group can be easily transformed into various important functionalities such as amines, aldehydes, carboxylic acids, etc.[181] Advantageously, these nitro-substituted alkenes are readily accessible by the nitro-aldol reaction.[182]

4.04.2.3.1 Addition of organozinc reagents

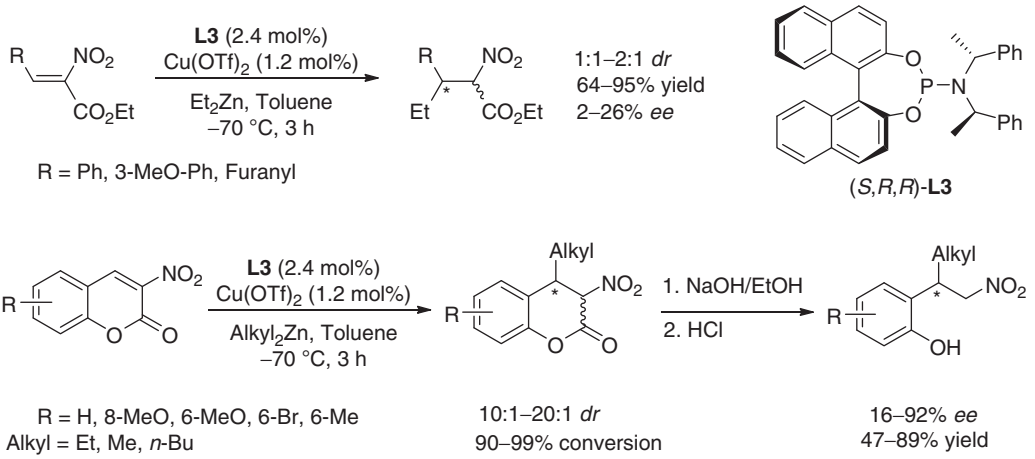
The first copper-based catalytic 1,4-addition (achiral) of dialkylzinc nucleophiles to α,β-unsaturated nitro-alkenes was reported by Alexakis et al. in 1997.[183] By reacting nitrostyrene and diethylzinc in the presence of 0.5 mol% of $Cu(OTf)_2$ and 1 mol% of trivalent phosphorus ligand $P(OEt)_3$, the expected racemic 1,4-adduct was isolated in 66% of yield. Inspired by these pioneering works, Sewald and Wendish were the first to report the enantioselective version of this methodology by involving the (*R,S,S*)-or (*S,S,S*)-phosphoramidite **L120a–b** as chiral ligands (Scheme 46).[184] Various solvents were screened at different temperatures (−78 to 0 °C) affording the corresponding nitro-alkanes in good to excellent conversions and moderate to good enantioselectivities (up to 86% *ee*).

In 1999, Feringa and coworkers described the enantioselective addition of dialkylzincs to various acyclic and cyclic α,β-unsaturated nitroacetates using the (*S,R,R*)-phosphoramidite **L3** ligand and copper(II)-triflate (Scheme 47).[185] The acyclic



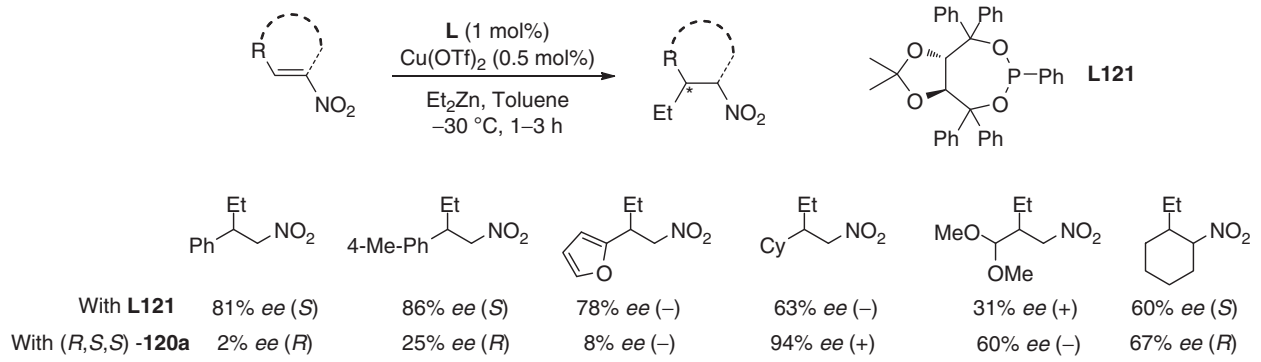
Scheme 46 The first enantioselective 1,4-addition of nitroolefins.

nitro-olefin substrates afforded the corresponding β-substituted nitroacetates in good isolated yields but with a diastereomeric ratio (*dr*) near 1:1 and extremely low *ee*s (<26%). Nevertheless, the cyclic 3-nitrocoumarin derivatives appeared more suitable, leading to the expected 1,4-adducts in higher dia- (up to 20:1) and enantioselectivities (up to 92%). Interestingly, after hydrolysis and decarboxylation, the β-aryl nitro-alkanes could be isolated in moderate to good isolated yields (47–89%) without racemization.



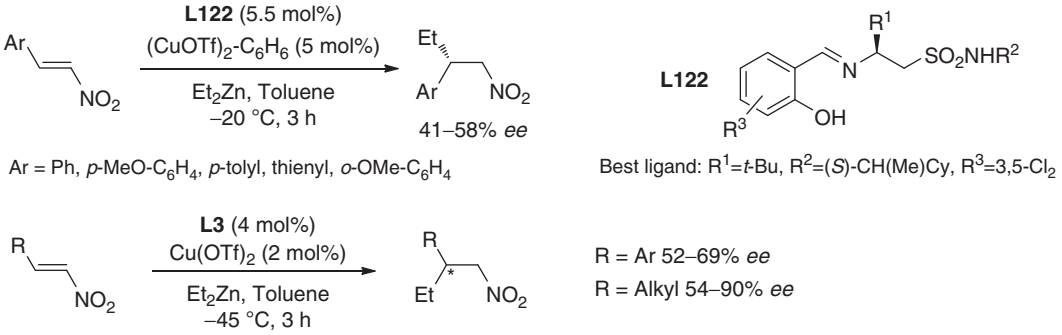
Scheme 47 1,4-Addition of acyclic and cyclic α,β-unsaturated nitroacetates.

In 2000, Alexakis and Benhaim screened nine chiral trivalent phosphorous-based ligands regarding the addition of dialkylzinc reagents (Me, Et, and *n*-Bu) to several di- or tri-substituted nitroolefins (Scheme 48).[186] Interestingly, this study highlighted clearly a significant variation of selectivity, depending on the nature of both the ligand and the Michael acceptors. Chiral ligand **L121** appeared the more efficient one considering aryl-substituted nitroolefins, with *ee*s as high as 86%. Nevertheless, this later was less efficient toward alkyl-substituted substrates (31–63% *ee*). On the contrary, the above-mentioned phosphoramidite (*R,S,S*)-**L120a** gave the highest enantioselectivity (94%) regarding alkyl-substituted nitroolefins, whereas quasi-racemic products were formed with nitro-styrene derivatives. Additionally, the case of dimethyl zinc was more problematic despite a full conversion in the corresponding β-methylated nitro-alkane, as only 20% of *ee* was observed.



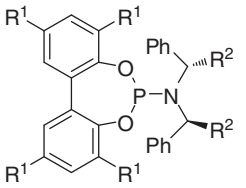
Scheme 48 Screening of phosphorous-based ligands for the 1,4-addition of aryl- and alkyl-substituted nitro-alkenes.

In the meantime, Gennari and coworkers proposed an efficient high-throughput screening of a parallel library of 10 Schiff-based ligands **L122** regarding the copper-catalyzed addition of diethylzinc toward nitro-stryrenyl derivatives (Scheme 49).[187] However, only low enantioselectivities were observed (<58% *ee*). Similarly, Feringa and coworkers reported a one-pot multi-substrate approach in the copper-phosphoramidite-catalyzed ACA of diethylzinc to different nitroalkenes.[188] As depicted in Scheme 49, up to eight phosphoramidite ligands and nine aromatic nitroolefins were screened in the meantime. Low to moderate *ee*s were obtained, ranging from 1% to 77%. However, the more efficient identified ligand (*S*,*R*,*R*)-**L3** afforded higher enantio-induction when aliphatic nitro-alkenes were involved (up to 90% *ee*).

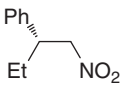


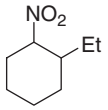
Scheme 49 Rapid screening of chiral ligands for the 1,4-addition of diethylzinc to aryl- and alkyl-substituted nitro-alkenes.

A dramatic improvement in enantioselectivities was noticed by Alexakis et al. in early 2002 (Scheme 50).[189] This was achieved through (1) the design of new phosphoramidite ligands **L7i,g,j** based on the atropoisomerically flexible biphenol unit and/or (2) the use of new experimental conditions (solvent and the nature of the copper source). The highest *ee*s were obtained with ligand **L7g** for the 1,4-addition of diethylzinc to nitrostyrene and nitrocyclohexene (82% and 95%, respectively).



(*S*,*S*)-**L7i**: R^1 = H, R^2 = Me)
(*S*,*S*)-**L7g**: R^1 = Me, R^2 = Me)
(*S*,*S*)-**L7j**: R^1 = H, R^2 = Et)



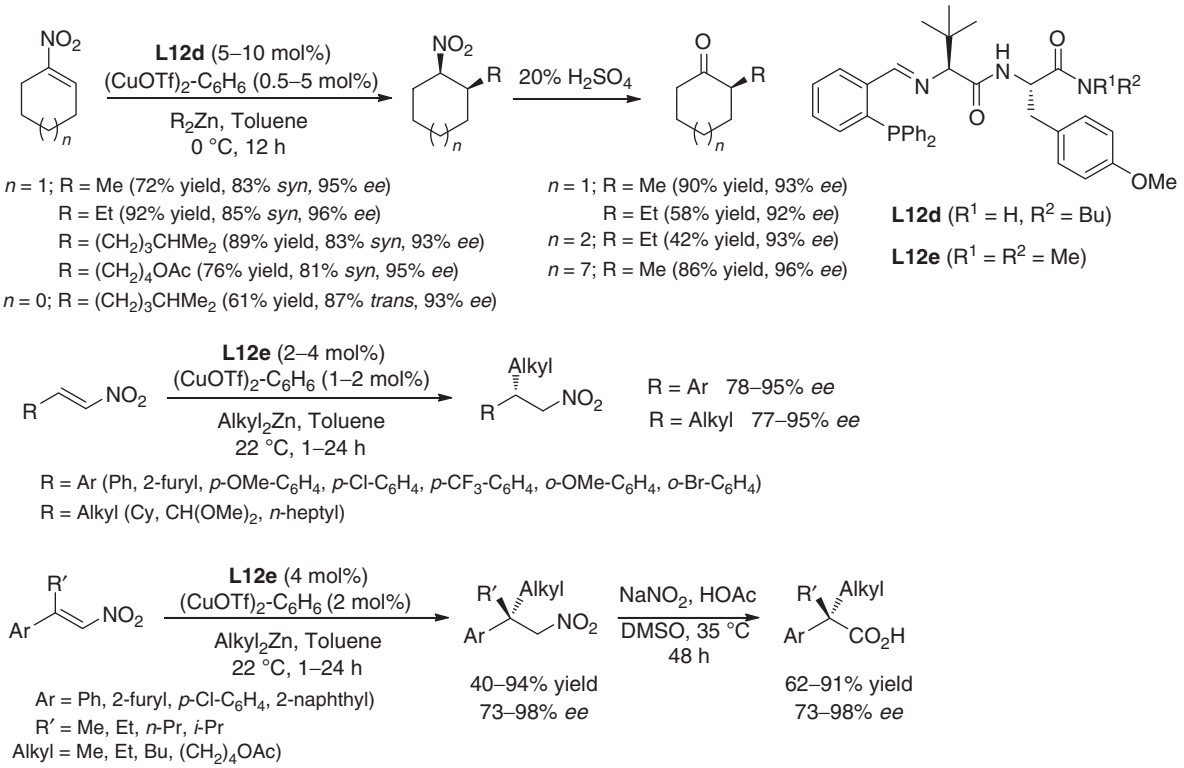


Optimized conditions	Conversion	*ee*
L7g (4 mol%) Cu(OAc)$_2$-H$_2$O (2 mol%) Et$_2$O, –30 °C, 3 h	>99%	82%
L7g (4 mol%) CuNapht. (2 mol%) Et$_2$O, –30 °C, 3 h	>99%	95%

Scheme 50 New ligand designs and modified experimental conditions for the 1,4-addition of diethylzinc to nitrostyrene and nitrocyclohexene.

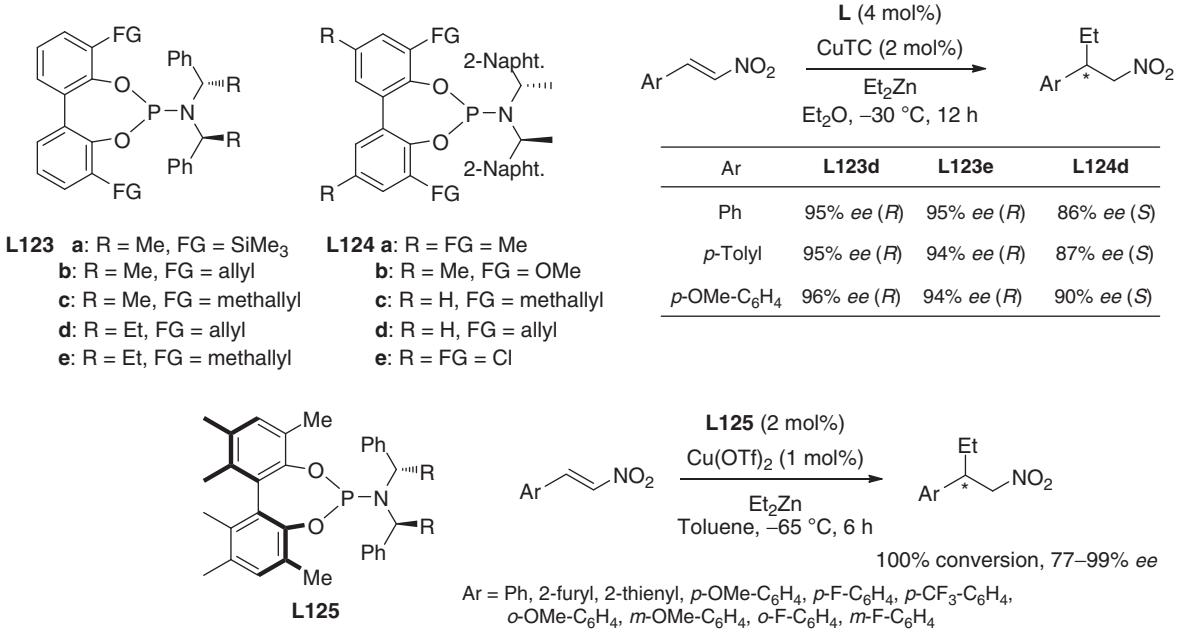
Significant breakthroughs were achieved by Hoveyda and Luchaco-Cullis with the use of 'small-peptide' diphenylphosphino-Schiff base ligands (Scheme 51). In the presence of copper(I)-triflate, the amino acid-based chiral ligands **L12d** catalyzed efficiently the enantioselective 1,4-addition of various dialkylzinc reagents, including notably the less reactive dimethyl zinc and carbonyl-containing alkylzinc, to five-, six-, seven-, and twelve-membered cyclic nitro-alkenes.[190] *Syn*-adducts were usually formed as major diastereoisomer (excepted for the five-membered substrate) with high enantioselectivities, ranging from 93% to 96%. Additionally, the resulting enantioenriched *β*-alkylated nitroalkanes were transformed into valuable cyclic ketones without any racemization. Later, this methodology was successfully extended to various aromatic and aliphatic acyclic nitroolefins by using a termini-modified ligand **L12e** (*ee*s ranged from 77% to 95%).[191] In 2005, this efficient chiral catalytic system was then applied to the first enantioselective synthesis of nitro-alkanes bearing all-carbon quaternary centers.[192] Moderate to good isolated yields (40–84%) and excellent selectivities (up to 98%) were obtained. Interestingly, the optically enriched 1,4-adducts were oxidized into corresponding carboxylic acids, which are not easily accessible through either asymmetric or diastereoselective alkylation of enolates.

To improve the enantioselectivity of the Cu-ACA of nitroolefins and extend the scope, several structural modifications on phosphoramidite ligands were attempted by a few groups. In 2004, Alexakis et al. designed a new class of monodentate



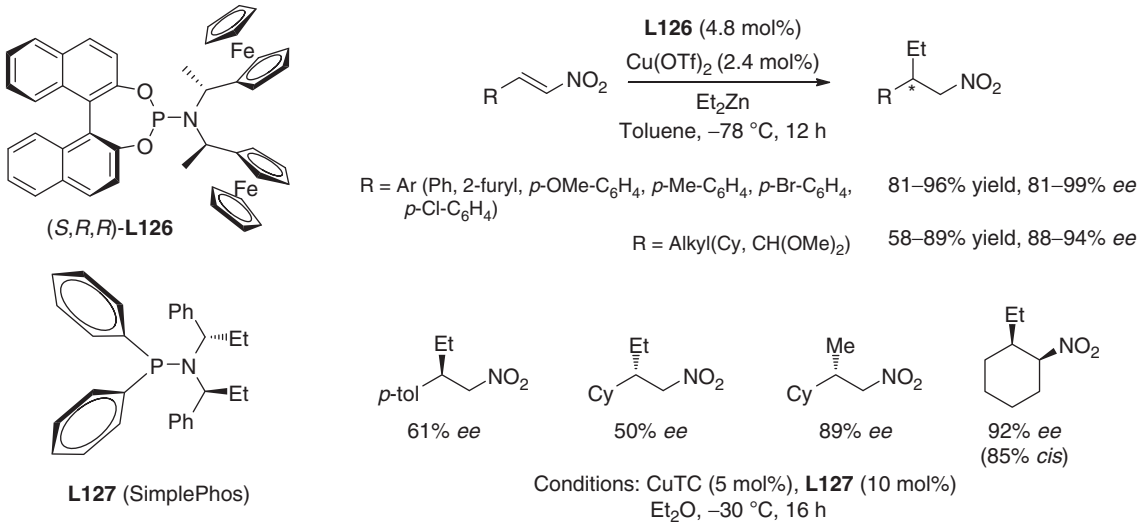
Scheme 51 Small-peptide ligands successfully used for the 1,4-addition of diethylzinc to cyclic and acyclic nitro-alkenes.

biphenol-based phosphoramidite ligands **L123**-**L124** by introducing different functions in *ortho-para*-position of the biphenol-unit[193] and by using new amine moieties (Scheme 52).[20] These slight structural modifications allowed reaching high *ee*s in the copper-catalyzed conjugate addition of diethylzinc to various nitroolefins (86–95% *ee*). In the meantime, Ojima and coworkers proposed a very close ligand **L125** (Scheme 52)[194] that appeared very efficient for various aromatic nitroalkanes, giving excellent *ee*s up to 99%.



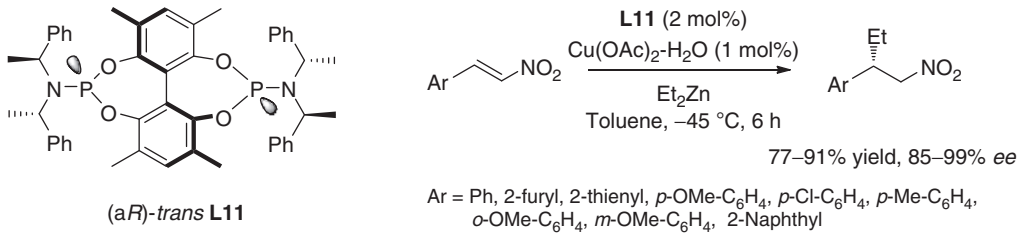
Scheme 52 Structural modifications on the biphenyl backbone in phosphoramidite ligands.

In 2009, Zheng and coworkers developed a ferrocene-based phosphoramidite ligand **L126** by using a chiral bis(1-ferrocenylethyl)amine (Scheme 53).[195] Interestingly, the chiral ferrocenyl moiety allowed reaching excellent *ee*s (from 88% to 99%) for various aromatic and aliphatic β-ethyl nitro-alkanes. In the meantime, Alexakis and coworkers proposed to replace the biphenol part by another type of chirality such as the helicity. This new conceptual ligand **L127**, called SimplePhos ligand, seemed quite efficient in copper-catalyzed 1,4-addition of cyclic enones, affording *ee*s up to 99%. However, in the case of nitroolefin, Michael acceptors, their efficiencies were less pronounced as a maximum of 92% of enantioselectivity was reached (Scheme 53).[83]



Scheme 53 Ferrocenyl-tagged phosphoramidite and SimplePhos ligands.

In 2010, inspired by the works of Alexakis and Ojima, Zhang et al. synthetized an atropos dibridged phosphoramidite ligand **L11** based on the D_2-symmetric biphenyl backbone (Scheme 54).[196] This D_2-symmetric ligand proved to be highly enantioselective in the 1,4-addition of diethylzinc to various aromatic nitroalkanes (*ee*s ranging from 85% to 99%).

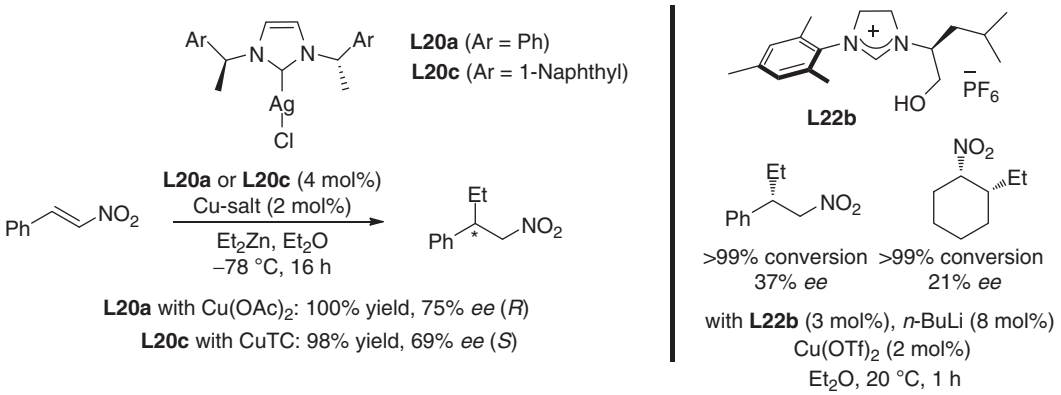


Scheme 54 D_2-symmetric atropos dibridged phosphoramidite ligand.

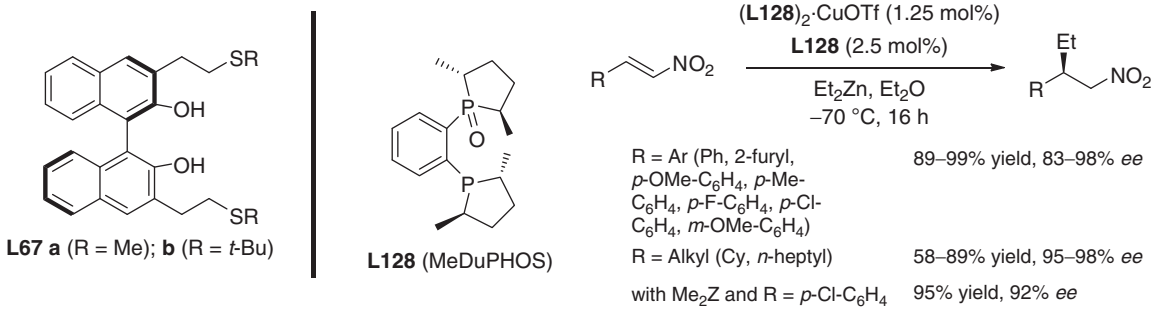
Phosphoramidite-, phosphite- and Schiff-based ligands were intensively studied in the Cu-catalyzed addition of diorganozinc nucleophiles to nitroalkenes. However, some other classes of chiral ligands such as NHC, binol-derivatives, or bis-phosphines were also investigated.

In 2003, Alexakis et al. were the first to report the use of chiral NHC ligands in the asymmetric synthesis of β-alkylated nitroalkanes (Scheme 55).[197] Among a small library of 11 NHC-type ligands, silver-NHC **L20a–L20c** appeared the highest enantioselective ligand for the copper-catalyzed addition of diethylzinc to nitrostyrene (69% and 75% *ee*, respectively). Later, Mauduit and coworkers evaluated the hydroxyalkyl-chelating NHC precursor **L22b** for the addition of diethylzinc to nitro-styrene and 1-nitro-cyclohexene.[198] Unexpectedly, although this class of NHCs was able to promote efficiently the addition of dialkylzincs to cyclic enones, only low enantio-inductions (<37% *ee*) were obtained regarding nitroolefins (Scheme 55).

However, BINOL-based thioether ligands **L67** were developed by Kang et al. in early 2003. However, only moderate enantioselectivities (<79%) were observed for the addition of diethylzinc to aromatic nitro-olefines (Scheme 56).[90] Remarkably, Charette and coworkers reported in 2007 the use of bis(phosphine) monoxides as hemi-labile ligands for the copper-catalyzed addition of dialkylzinc reagents to β-nitroalkenes (Scheme 56).[199] Indeed, after a screening of Me-DuPHOS and its mono- and di-oxide derivatives, the Me-DuPHOS monoxide **L128** appeared the most efficient ligand, providing efficiently various enantioenriched β-alkylated nitroalkanes with *ee*s up to 98%.

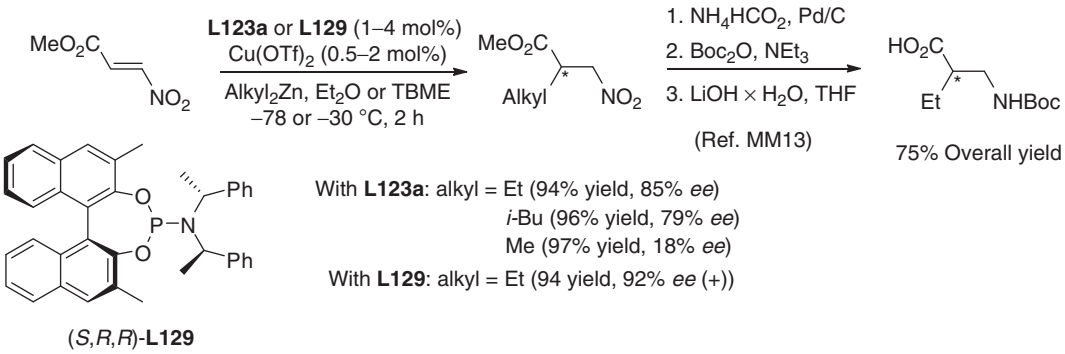


Scheme 55 NHC ligands used for the 1,4-addition of diethylzinc to cyclic and acyclic nitro-alkenes.



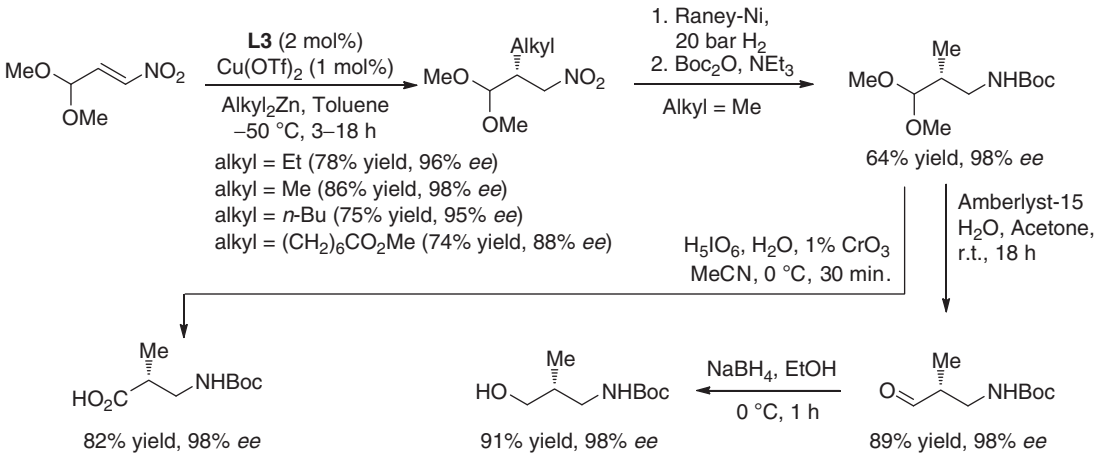
Scheme 56 BINOL-based thioether and Me-DuPHOS monoxide in 1,4-addition of dialkylzinc to cyclic and acyclic nitro-alkenes.

As the nitro group can be easily converted into the corresponding carboxylic acid, some useful asymmetric synthetic applications were envisaged. In 2003, Sewald and Rimkus[200] and Wendish[201] independently reported the first enantioselective synthesis of β^2-amino acids by using the Michael addition of diorganozinc reagents to nitroacrylates catalyzed by enantiopure phosphoramidite-based ligands (Scheme 57). When the Feringa's ligand (*S,S,S*)-**L120b** was involved, up to 79% and 85% *ee* were obtained for the addition of diisobutyl- and diethyl-zinc to methyl-3-nitropropionate, respectively. The resulting adducts were transformed into corresponding amino acids through a hydrogenation/saponification sequence without any racemization. Sewald obtained higher enantioselectivity (up to 92%) with the binol-modified phosphoramidite (*S,R,R*)-**L129**, leading to the desired Boc-protected β^2-amino acid after a three-step process in 75% overall yield.



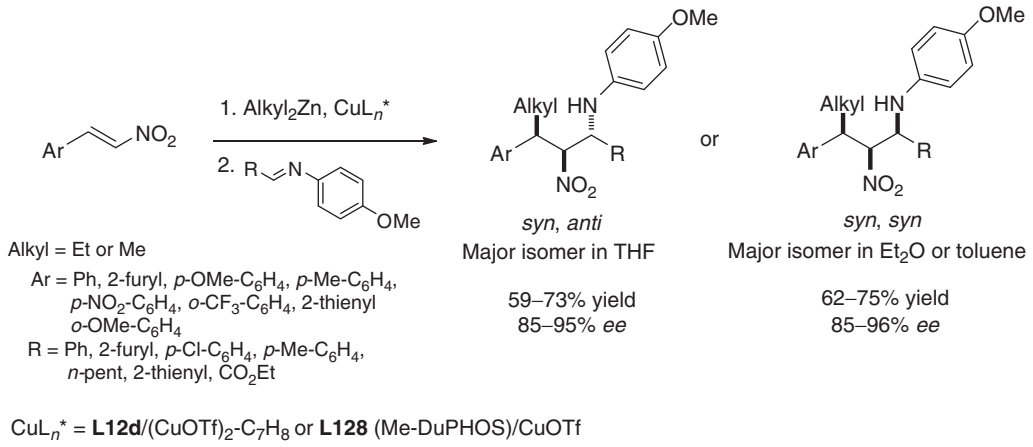
Scheme 57 Enantioselective route to β^2-amino acids through the Michael addition of diorganozinc reagents to nitroacrylates.

In the meantime, Feringa and coworkers proposed an alternative catalytic route to provide β^2-amino acids and derivatives by employing nitropropene acetals (Scheme 58).[202] (*S,R,R*)-**L3** showed remarkable high *ee*s for the 1,4-addition of various dialkylzinc, ranging from 88% to 98%. The resulting enantioenriched nitroalkanes were easily converted into protected β^2-amino acids, aldehydes, and alcohols that represent valuable building blocks for total synthesis.



Scheme 58 Alternative routes to enantioenriched β^2-amino acids and derivatives involving nitropropene acetals.

Recently, Anderson et al. reported an efficient one-pot enantioselective copper-catalyzed conjugate addition nitro-Mannich reaction protocol combining dimethyl- or diethyl-zinc, aromatic nitro-alkenes, and imines to form two C–C bonds and three contiguous centers (Scheme 59).[203] The stereoselectivity was controlled from the initial 1,4 addition catalyzed by small-peptide **L2d**/$(CuOTf)_2$-C_7H_8 or by Me-DuPHOS **L128**/CuOTf, whereas either the *syn*, *anti* or *syn*, *syn* disatereoisomers were controlled by the solvent. Therefore, various acyclic *anti*- and *syn*-β-nitroamines were synthetized with moderate to good yields (59–73%) and excellent *ee*s, ranging from 85% to 96%.

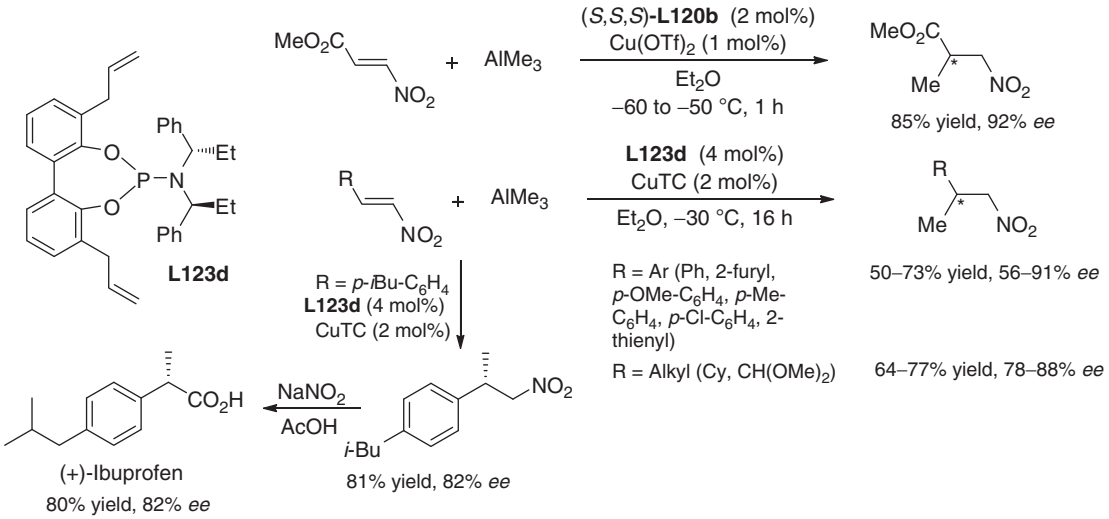


Scheme 59 Stereoselective synthesis of acyclic *anti*- and *syn*-β-nitroamines through the one-pot copper-catalyzed conjugate addition/nitro-Mannich reaction protocol.

4.04.2.3.2 Miscellaneous C-nucleophiles

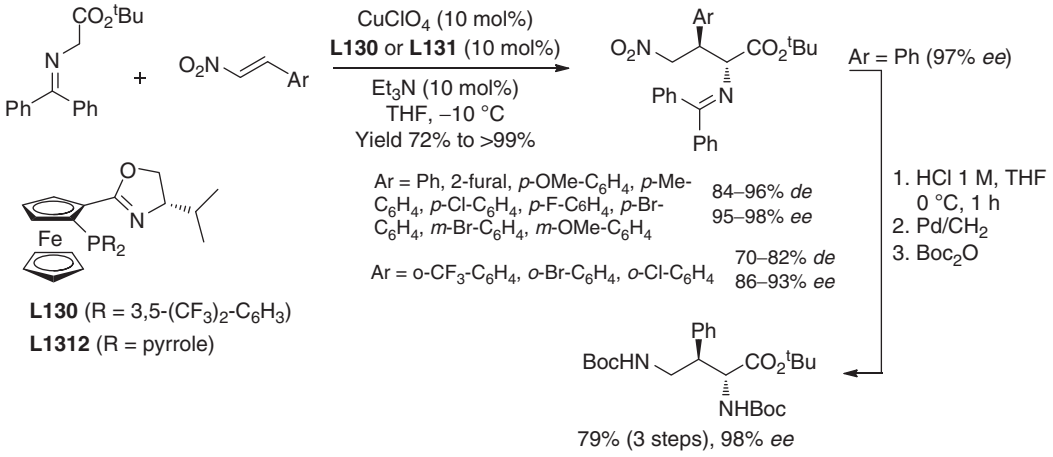
Unlike dialkylorganozinc nucleophiles that have been intensively studied for the copper-catalyzed 1,4-addition of nitroalkene Michael acceptors, only two examples were described concerning the use of trialkyl aluminum and none with Grignard reagents until now. The first report was accomplished by Wendish and coworkers in 2003 that involved nitro-acrylates and trimethyl aluminum as reactants in the presence of Feringa's ligand (*S*,*S*,*S*)-**L120b** and copper(II)-triflate (Scheme 60).[204] The resulting 2-methyl-3-nitro propionic acid esters were obtained on a 200 g scale with *ee*s up to 92%. Two years later, Alexakis and Polet proposed to extend this methodology to various aromatic and aliphatic nitroolefines (Scheme 60).[205] Phosphoramidite ligand **L123d** was found the best ligand in association with copper thiophenecarboxylate (CuTC) under optimized conditions (Et_2O, −30 °C, 16 h). Enantioenriched nitro-alkanes were isolated in moderate to good yields (50–77%) and *ee*s (56–88%). Interestingly, this asymmetric catalytic process was successfully applied to the synthesis of (+)-ibuprofen with 65% of yield (two steps) and 82% *ee*.

In 2010, few metal-free C-nucleophiles were also investigated for the copper-catalyzed Michael addition to nitroolefins allowing producing, in a straightforward route, highly functionalized chiral building blocks that are strongly desirable for organic synthesis. For instance, Hou and coworkers described the first enantioselective addition of glycine derivatives to various aromatic nitro-alkenes catalyzed by $CuClO_4$ in the presence of ferrocenyl-based ligand **L130** (Scheme 61).[206] The resulting 1,4-adducts were



Scheme 60 First examples of copper-catalyzed 1,4-addition of trimethyl aluminum nucleophiles to nitro-alkenes.

isolated in excellent yields (>99%) and remarkable *ee*s (95–97%) excepted for *ortho*-substituted aromatic adducts (64–89% *ee*). To circumvent this, a new 1,2-*P*,*N*-ferrocene ligand **L131** was designed affording the reluctant adducts with higher enantioselectivities (86–93%). Interestingly, enantioenriched 1,4-adducts were efficiently converted into highly valuable *β*-substituted-*α*,*γ*-diaminobutyric acid derivatives.



Scheme 61 Asymmetric 1,4-addition of metal-free C-nucleophiles to nitro-alkenes.

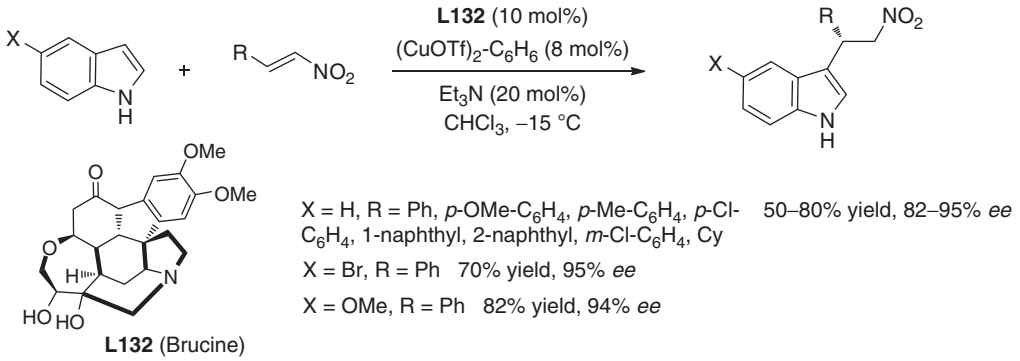
In the meantime, Oh and coworkers proposed an original and promising 1,4-addition of indoles to various nitroalkenes (Scheme 62).[207] This 'Friedel–Crafts alkylation of indoles,' catalyzed by copper(I) salts in the presence of the brucine-derived ligand **L132**, led to corresponding 1,4-adducts in moderate to good yields (52–85%) and excellent enantioselectivity (up to 95%).

The last example involving metal-free nucleophiles was reported by Sodeoka and coworkers disclosing the ACA of *α*-keto esters to aromatic nitroolefins (Scheme 63).[208] Copper(II) hydroxo-complex bearing chiral *N*-substituted diaminocyclohexane **L133** could be used as a mild and selective acid-base catalyst, affording corresponding cross-coupling 1,4-adducts in moderate to good isolated yields (45–86%) with a total *anti*-stereochemistry and good *ee*s up to 84%.

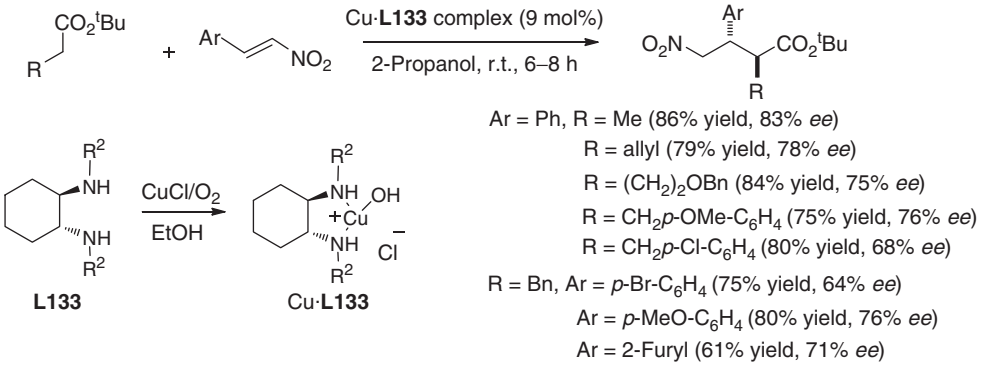
4.04.2.4 Miscellaneous Michael Acceptors

4.04.2.4.1 Piperidones and pyridones

The piperidine moiety is an important structural feature in many medicinal compounds. As a strategy to make pharmacomodulations around this ring, the copper-catalyzed enantioselective addition of piperidones or pyridones was explored. Feringa and Minnaard reported that the powerful system $Cu(OTf)_2$ and binaphtyl-based phosphoramidite such as **L3** was able to achieve the addition of dialkylzinc reagents to 2,3-dehydro-4-piperidones with *ee*s reaching high values (Scheme 64).[209] Yields were found

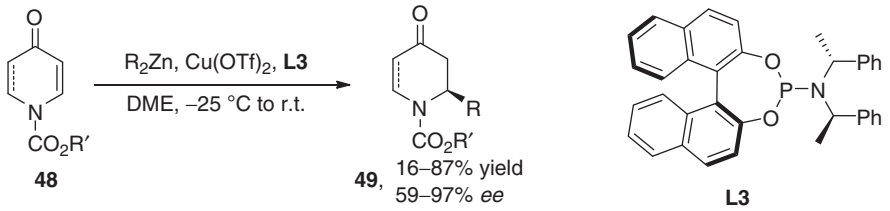


Scheme 62 Enantioselective copper-catalyzed Friedels–Crafts alkylation of indoles.



Scheme 63 Enantioselective Michael addition of α-keto esters to aromatic nitro-alkenes.

fluctuating because of difficulty in purifying the products. To prove the synthetic potential of this ACA, the synthesis of the alkaloid (+)-myrtine was achieved. Dieter and Guo showed that the same system could be applied to pyridones but with slight drop of *ee*s (81%).[210] Pyridones and piperidones are easily synthesized from 4-methoxypyridine; however, Feringa and Minnaard demonstrated that 4-methoxypyridine could be converted into *N*-acylpyridinium salts and *in situ* treated with dialkylzinc in the presence of copper salt and phosphoramidite ligand to give the adduct piperidone with *ee*s up to 97%.[211]

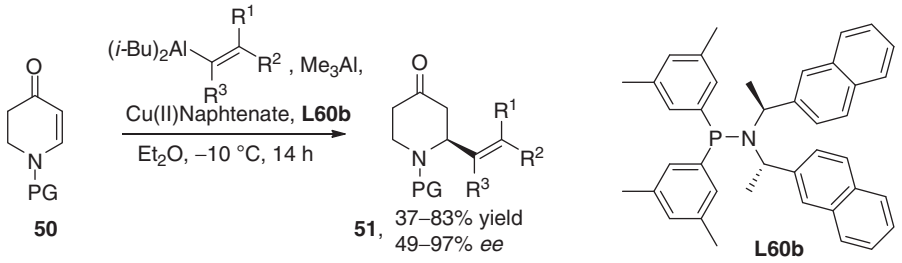


Scheme 64 Copper-catalyzed ACA of dialkylzinc to piperidones or pyridines.

Alexakis explored alkenyl alanes instead of alkylzinc reagents as C-nucleophiles.[212] As depicted in Scheme 65, a Cu(II) naphtenate salt which is a very inexpensive copper complex has been used in association with phosphine amine ligand **L60b** which was found superior to phosphoramidites, phosphines, or ferrrocenyl-based ligands in terms of both activity and enantioselectivity. This reaction required a coactivation with $AlMe_3$ acting as Lewis acid but the use of ethereal solvent avoided the competitive methyl transfer. Thus, piperidinones **51** were isolated generally with moderate yields but excellent *ee*s.

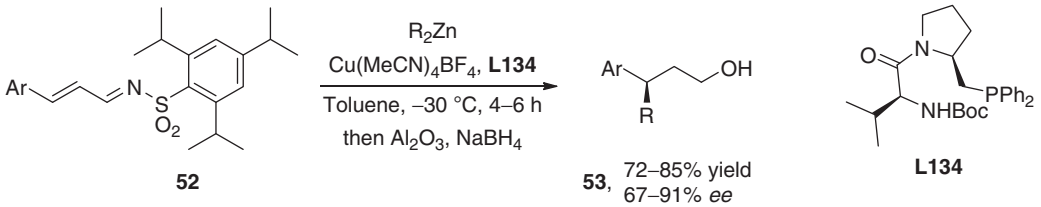
4.04.2.4.2 α,β-Unsaturated imines

In 2005, independently Tomioka and coworkers[213] and Carretero and coworkers[214] described the copper-catalyzed ECA of dialkylzinc reagents to α,β-unsaturated imines with a different goal. Carretero wished to broaden the ACA scope to this class of Michael acceptors and circumvented metal poisoning issues using a ketenimine bearing a (2-pyridyl)sulfonyl group as electron-withdrawing group. With phosphoramidite **L3** and copper(I) thiophencarboxylate, the addition of Me_2Zn was achieved with good yields and *ee* ranging from 71% to 80%. To solve problems encountered with conjugate addition to α,β-unsaturated aldehydes,



Scheme 65 Cu-mediated ACA of alkenyl alane to 2,3-dehydro-4-piperidones.

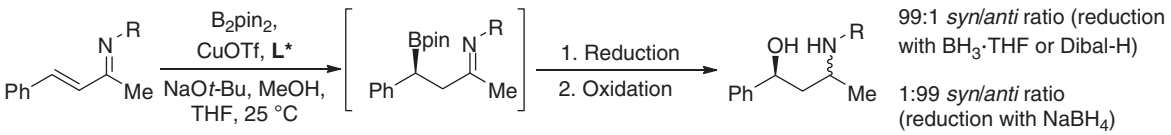
that is preferentially 1,2-addition, Tomioka investigated aldimines (Scheme 66). 2,4,6-Triisopropylphenylsulfonylimine was selected as masking group of aldehyde function because steric congestion favored 1,4-addition. A combination of copper(I) salt and the amidophosphine **L134** allowed to get alcohols **53** in good yields with moderate to high optical purity.



Scheme 66 Asymmetric Cu-catalyzed conjugate addition of R_2Zn to α,β-unsaturated aldimines.

Palacios addressed the problem of imine-metal coordination leading to an absence of reactivity by an alternative approach.[215] α,β-Unsaturated imine substrates containing an extra deactivating ester group were used and allowed the synthesis of γ-substituted α-dehydroaminoesters with *ee*s up to 88% induced by a TADDOL-derived phosphoramidite ligand.

As a strategy to prepare optically pure γ-amino alcohols, Gulyás and Fernández explored the β-boration of α,β-unsaturated imines.[216] As presented in Scheme 67, a highly enantioselective and diastereoselective one-pot Cu-promoted β-boration/reduction/oxidation process was developed to get amino alcohols **56**. The asymmetric β-boration was found to be very substrate-dependent and each imine **54** required a ligand screening to point out the best chirality inducer, respectively Taniaphos, Josiphos **L86**, and a phosphoramidite. As a function of the reducing agent, it was also possible to favor the formation of either the *syn* or the *anti* diastereomer.



54a, R = Bn
54b, R = Ph
54c, R = *n*-Bu

55a, 99% *ee*
55b, 92% *ee*
55c, 93% *ee*

56a, 67–90%
56b, 69%
56c, 92%

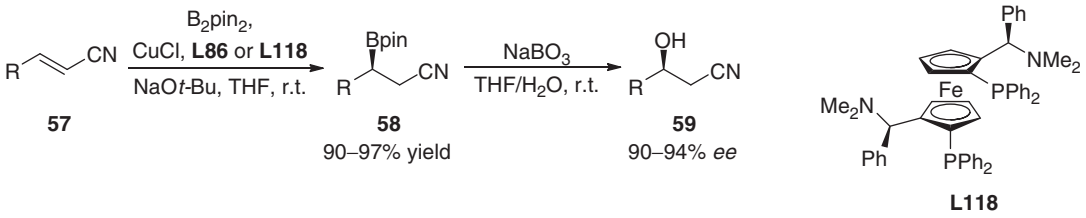
Scheme 67 Preparation of γ-amino alcohols by Cu-catalyzed enantioselective β-boration of α,β-unsaturated imines.

4.04.2.4.3 α,β-Unsaturated nitriles

α,β-Unsaturated nitriles are a recalcitrant class of Michael acceptors for conjugate addition of C-nucleophiles. To the best of our knowledge, only few examples are described in the literature. As presented above, Hayashi and Shintani disclosed the enantioselective 1,4-addition of organoboronates to alkylidene cyanoacetates **26**.[160] When Yun worked on the asymmetric boration of acyclic α,β-unsaturated esters, he first considered cinnamonitrile as benchmark substrate and several α,β-unsaturated nitriles **57** were tested during the scope examination giving excellent enantiomeric inductions (Scheme 68).[175a,b]

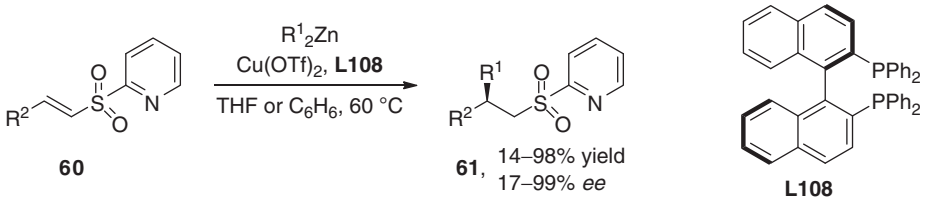
4.04.2.4.4 Vinyl sulfones

As an alternative to ACA, so called 1,4-hydrosylilation, of β,β-disubstituted α,β-unsaturated sulfones, Charette and Bechara developed the enantioselective addition of dialkylzinc reagents to vinyl sulfones for the synthesis of sulfones bearing β stereocenters.[217] To achieve this goal, various bidendate chiral ligands were screened and the best results were obtained with (*R*)-BINAP **L108** (Scheme 69). At room temperature, conversions were found to be low but could be improved by carrying out reactions at



Scheme 68 Cu-mediated asymmetric boration of α,β-unsaturated nitriles.

higher concentration and/or higher temperature without impacting *ee* values. The scope of conjugate addition was found good with yields and enantiomeric excesses 55–93% and 84–98%, respectively, except for the α-branched organozinc reagent where it dropped to 14% yield and 17% *ee*. Later, Feringa and coworkers showed that the same catalytic system with phosphoramidite **L3** was able to give β-substituted sulfones **61** with good to excellent stereoinduction even when diisopropylzinc was used as C-nucleophile.[218] Nevertheless, (*R*)-BINAP **L108** proved to be the most efficient ligand for Grignard reagent addition to α,β-unsaturated sulfones with *ee* up to 94%.[219]

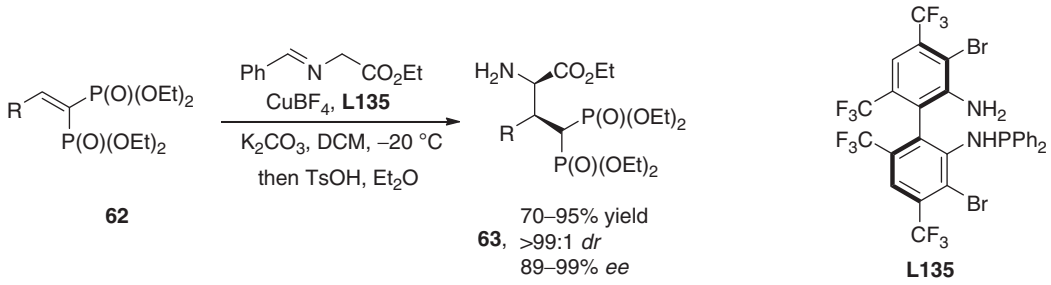


Scheme 69 Copper-catalyzed enantioselective addition of diorganozinc reagents to vinyl sulfones.

The applicability range of the combination copper salt with (*R*)-BINAP **L108** was then widened to asymmetric conjugate boration of α,β-unsaturated sulfones giving after oxidation β-hydroxy sulfones with high optical purity.[220]

4.04.2.4.5 α,β-Unsaturated phosphates

In spite of the large number of catalytic enantioselective Michael additions in organic synthesis, alkylidene phosphonate derivatives have been scarcely investigated and mostly with organocatalysts. In 2011, Wang and coworkers described a novel catalytic asymmetric enantioselective Michael addition of azomethine ylide with β-substituted alkylidene bisphosphates **62** (Scheme 70).[221] Interestingly, the reactivity of azomethine ylide was found to be a function of the Michael acceptors. Acrylate derivatives, alkylidene malonates, and β-substituted vinylidenecarboxyalte-phosphonates afforded [3+2]-cycloadducts, whereas vinylphosphonates were found to be unreactive. Only alkylidene bisphosphates were subjected to Michael additions and with the adequate reaction conditions, that is $Cu(MeCN)_4BF_4$, ligand TF-Biphamphos **L135** with K_2CO_3 as a base in catalytic amount in DCM at low temperature. Michael adducts were then treated with *p*-toluenesulfonic acid to give various α-amino acid derivatives **63** with both excellent diastereomeric and enantiomeric ratios.

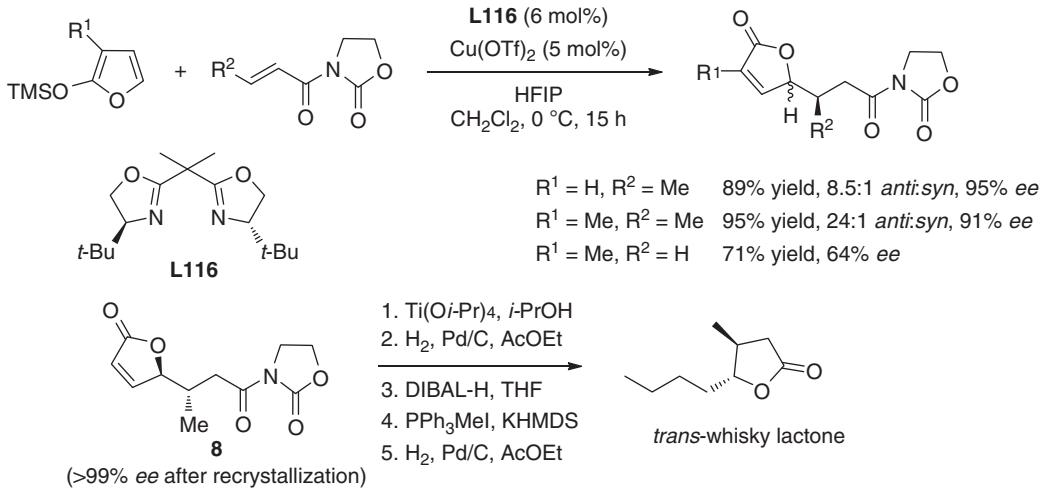


Scheme 70 Copper-promoted direct asymmetric Michael addition to alkylidene bis(phosphonates).

4.04.2.4.6 α,β-Unsaturated imides

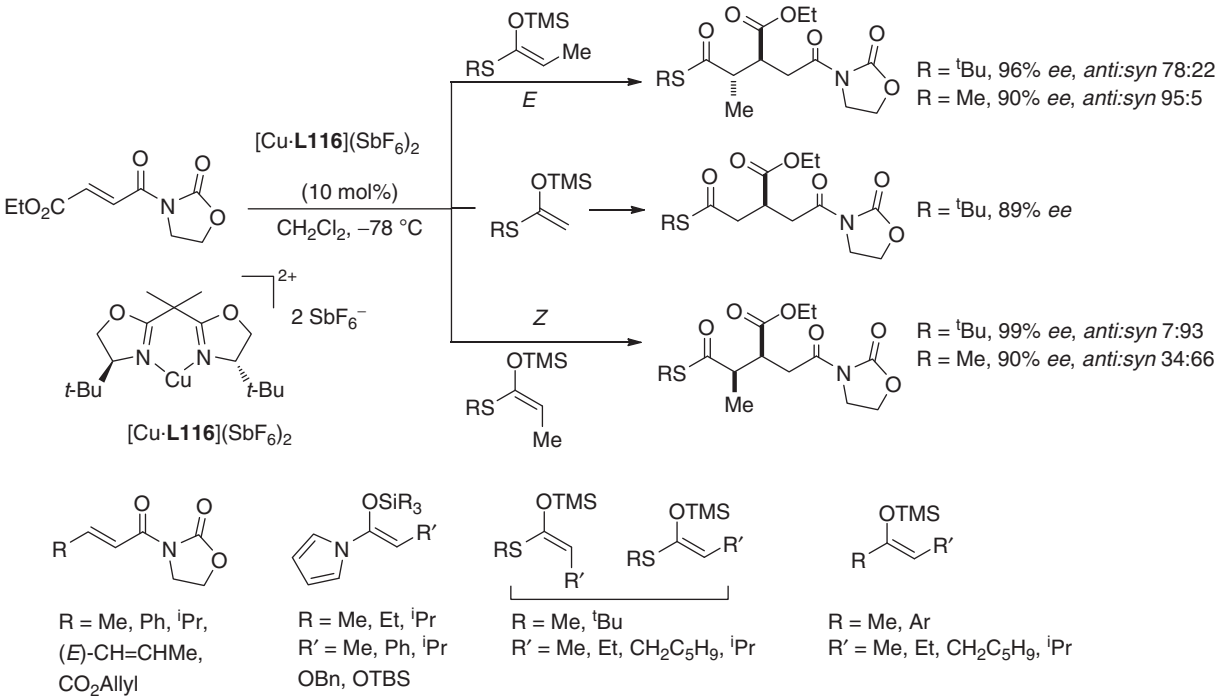
Curiously, contrary to various other Michael acceptors, the α,β-unsaturated imides were first investigated with metal-free (soft) nucleophiles in asymmetric copper-catalyzed conjugate addition. Katsuki and Nishikori were the first to report in 1997 this methodology with the enantioselective addition of 2-(trimethylsilyloxy)furans to the crotonyl oxazolidinone (e.g., crotoyl imide)

catalyzed by the well-known Lewis acid copper complex $Cu(OTf)_2$/bis-oxazoline **L116** (Scheme 71).[222] Excellent enantioselectivity (up to 95%) and moderate to good *anti*-selectivity (8.5:1–24:1) were obtained. It was notified that addition of hexafluoro-2-propanol (HFIP) was required to achieve high chemical yields. This efficient catalytic protocol was then applied to the enantioselective synthesis of *trans*-whisky lactone, which was isolated in only six steps from the enantiopure Michael *anti*-adduct.[223]



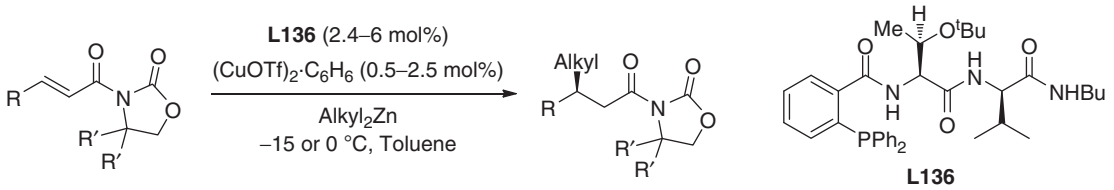
Scheme 71 Copper-catalyzed enantioselective addition of 2-(trimethylsilyloxy)furans to the crotoyl imide.

One year later, Evans et al. used the Katsuki protocol for the addition of thioester enolsilanes to fumaroyl imides (Scheme 72).[224] Excellent yields (93–99%) and enantioselectivities (90–99% *ee*) were reached with the copper-complex [Cu·**L116**]$(SbF_6)_2$. The sense of the diastereoselection was directly connected to the enolsilane geometry: *anti*-adducts were preferably formed from *E*-enolsilane, whereas *Z*-enolsilane afforded *syn*-adducts. Remarkably, this methodology was successfully extended to various functionalized enolsilanes and substituted acrylimides with excellent *ee*s (67–99%).[225]



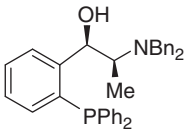
Scheme 72 Copper-catalyzed enantioselective addition of various functionalized enolsilanes to fumaroyl and crotoyl imides.

Hoveyda and Hird were the first to report in 2003 the 1,4-addition of alkyl-metal nucleophiles to α,β-unsaturated imides (Scheme 73).[226] The chiral triamide phosphane ligand **L136** in association with copper(I)-triflate complex catalyzed efficiently the addition of dialkylzinc to various unsaturated oxazolidinone in high isolated yields and excellent enantioselectivity (up to >98%). Additionally, the resulting enantioenriched β-alkylated *N*-acyloxyoxazolidinones may be converted into carbonyl derivatives (ketone, Weinreb amide, or carboxylic acid) in good yields and without alteration in the *ee*s. Later, the group of Nakamura observed a similar high enantioselectivity (98.7% *ee*) with a newly designed aminohydroxyphosphine ligand **L137** for the addition of diethylzinc to crotonyl oxazolidinone (91% yield) (Scheme 73).[59]



with R′ = H R = Me, *n*Pr, $(CH_2)_3OTBS$, *i*Pr Alkyl = Et, Me, *i*Pr$(CH_2)_3$ 61–95% yield, 76 to >98% *ee*

with R′ = Me R = Ph Alkyl = Et 91% yield, 86% *ee*



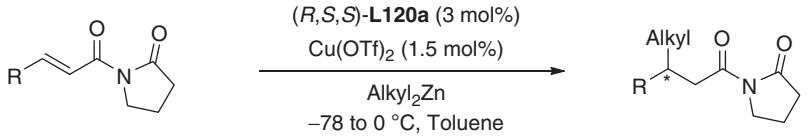
L137

With **L137** (6 mol%)/$Cu(OTf)_2$ (5 mol%)

R′ = H, R = Me, Alkyl = Et 91% yield, 98.7% *ee*

Scheme 73 Copper-catalyzed enantioselective addition of dialkylzincs to α,β-unsaturated *N*-acyloxazolidinones.

In 2006, Pineschi et al. screened various crotonic imides as Michael acceptors for the copper-phosphoramidite (*R*,*S*,*S*)-**L120a**-catalyzed addition of diethylzinc (Scheme 74).[227] Although the oxazolidinone moiety, successfully used by Hoveyda, gave only 64% *ee*, the highest enantioselectivity (87%) was reached with the 2-pyrrolidinone fragment. The scope was then extended to various α,β-unsaturated *N*-acyl-2-pyrrolidinones and dialkylzinc reagents giving corresponding 1,4-adducts in low to good yields (7–88%) and good to excellent *ee*s (60 to >99%). Further attempts at using the trimethylaluminum reagent were unsuccessful as low *ee*s were reached (20–36% *ee*).



R = Me, Pr, *i*Pr, (*E*)-CH_3CH=CH, 1-cyclohexenyl Alkyl = Et, *i*Pr 7–80% yield, 60–96% *ee*

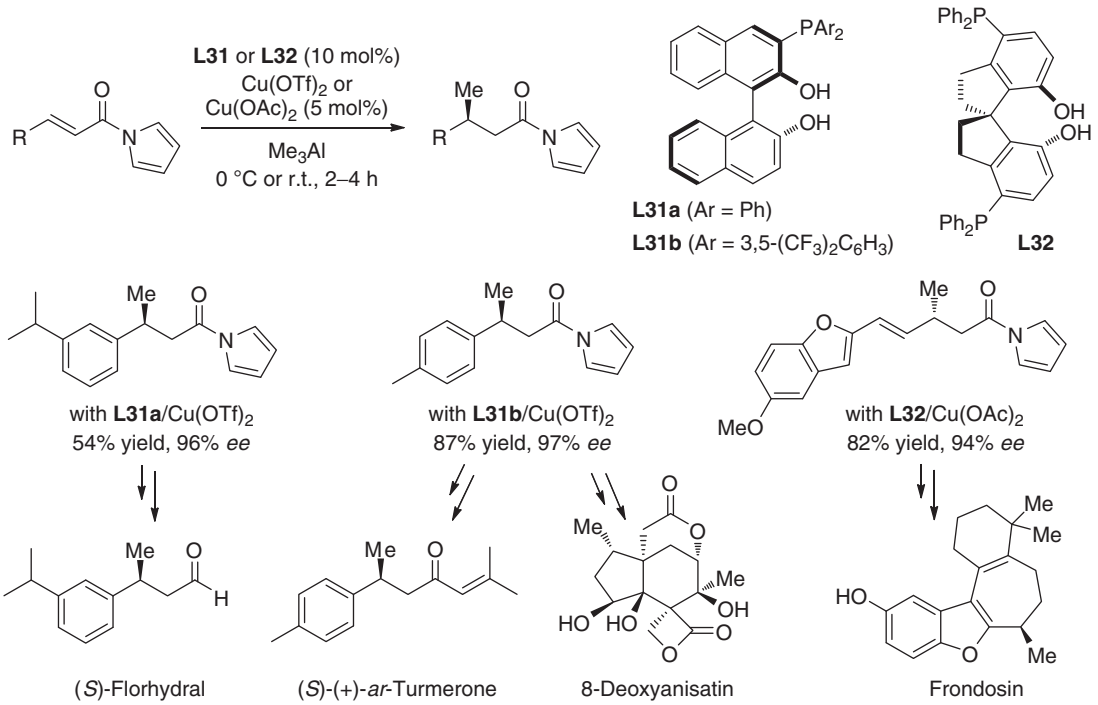
R = Ph, *p*-BrC_6H_4, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *p*-$CF_3C_6H_4$, *m*-$CF_3C_6H_4$, *o*-BrC_6H_4, *o*-MeC_6H_4 Alkyl = Et, *i*Pr, Bu 44–88% yield, 80 to >99% *ee*

Scheme 74 Enantioselective copper-catalyzed addition of dialkylzincs to α,β-unsaturated *N*-acyl-2-pyrrolidinones.

In 2012, Endo and Shibata described a powerful catalytic system based on multinuclear copper/aluminum complexes promoting the efficient enantioselective addition of trimethylaluminum to *N*-acylpyrrole derivatives (Scheme 75).[228] This methodology using phenol-phosphine-based ligands **L31a–b** and **L32** allowed to synthesize various natural molecules such as (*S*)-florhydral and (*S*)-(+)-*ar*-turmerone or key intermediates in the synthesis of 8-deoxyanisatin and frondosin.

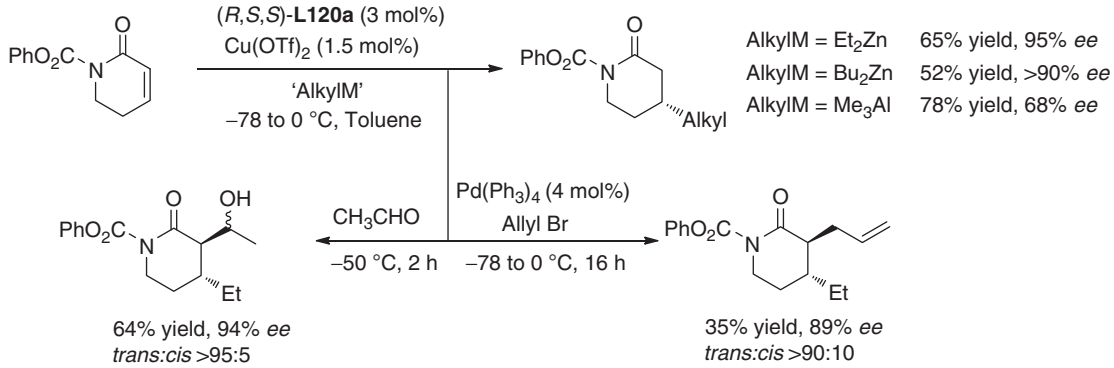
4.04.2.4.7 α,β-Unsaturated lactames

To the best of our knowledge, only one example of copper-catalyzed ACA of organometallic reagents to α,β-unsaturated lactames has been reported in the literature till now. This is probably because of the inherent low reactivity of this kind of Michael acceptor. In 2004, Pineschi and coworkers jointly demonstrated that the use of appropriate protecting-activating carbamate groups allowed overcoming the lack of reactivity of α,β-unsaturated lactames (Scheme 76).[229] By using catalytic amounts of phosphoramidite ligand (*R*,*S*,*S*)-**L120a** and copper(II)-triflate, moderate to good yields (52–65%) and excellent enantioselectivities (90–95%) were reached for the addition of diethyl- and dibutyl-zinc reagents to the α,β-unsaturated lactame protected with a carbophenoxy group. The unreactivity of dimethylzinc observed in this reaction protocol was compensated by the use of the trimethylaluminum



Scheme 75 Enantioselective copper-catalyzed addition of trimethylaluminum to *N*-acylpyrrole derivatives.

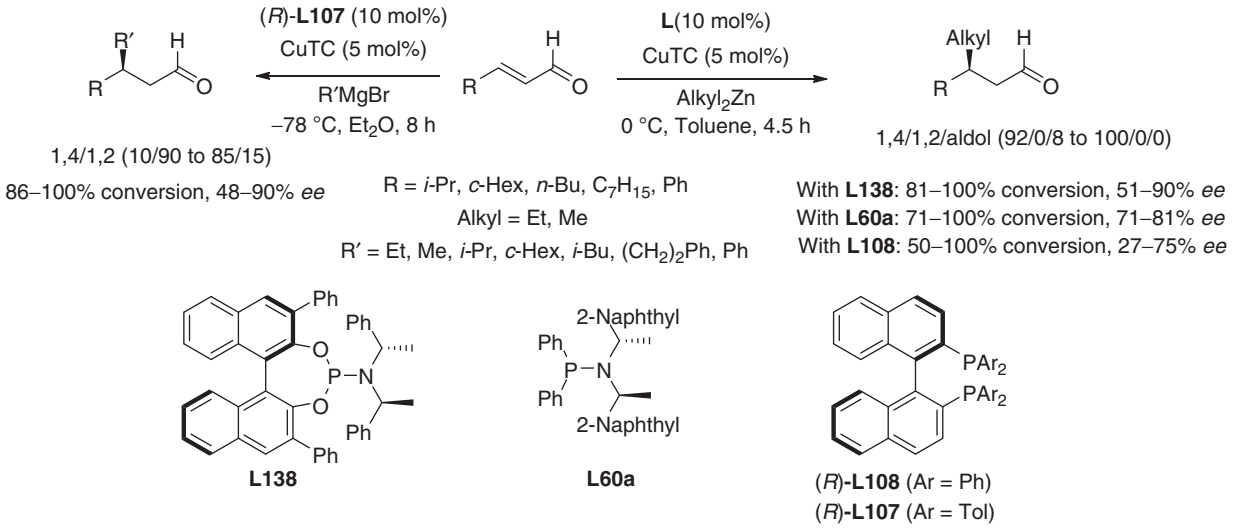
reagent, which afforded the valuable β-methylated adduct in 78% of yield and 68% *ee*. Interestingly, the intermediate zinc enolate could be trapped with acetaldehyde or with allyl bromide to deliver the corresponding α,β-disubstituted lactames in 94% and 89% *ee*, respectively.



Scheme 76 First copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated lactames.

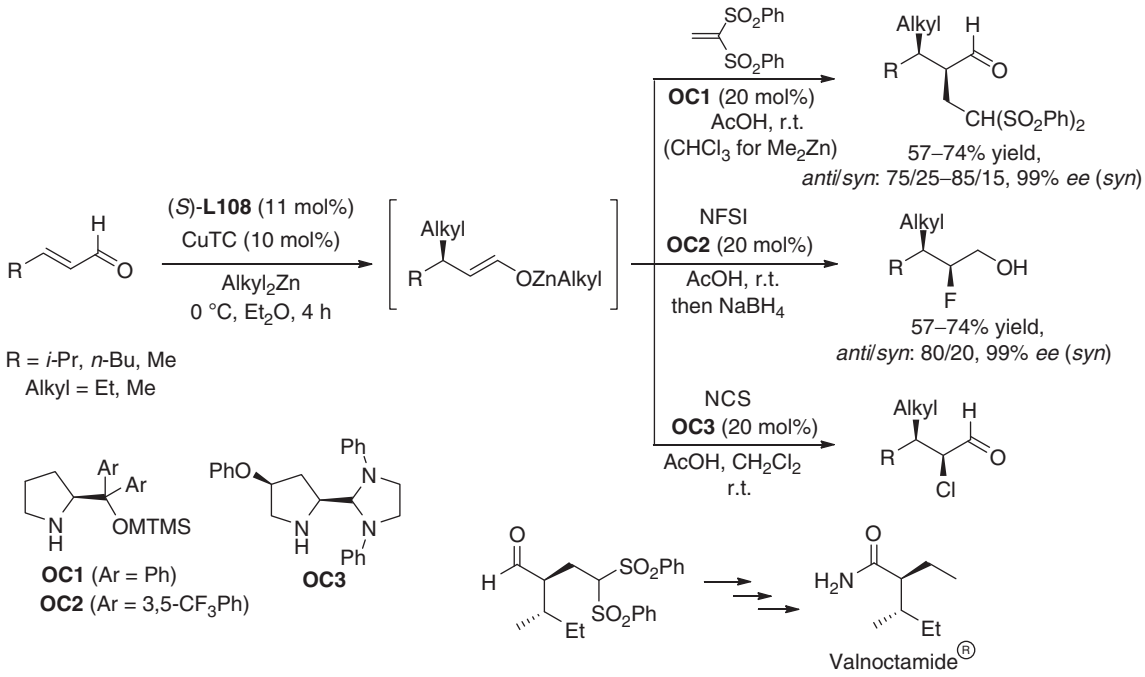
4.04.2.4.8 α,β-Unsaturated aldehydes

α,β-Unsaturated aldehydes represent certainly the most challenging Michael acceptor concerning the asymmetric copper-catalyzed conjugate addition of organometallic nucleophiles. This is mainly because of their higher reactivity that allows the undesired formation of 1,2-adducts as well as the aldol by-product. In 2005, Bräse and Höfener described an enantioselective copper-free 1,4-addition of organozinc reagents to enals.[230] In the meantime, racemic and diastereoselective versions promoted by a catalytic amount of lithio cyanocuprate were successfully reported by Marshall.[231] Four years later, Alexakis and coworkers were the first to report the copper-mediated enantioselective version of this catalytic reaction involving both dialkylzinc and Grignard reagents.[232] After a screening of various chiral ligands in the presence of copper(II)-thiophene carboxylate, phosphoramidite **L138**, SimplePhos **L60a** and (*R*)-BINAP **L108** appeared the highest regio- and enantioselective ligands for the addition of diethyl- and methylzinc, with 1,4-selectivities reaching up to 100% (Scheme 77). The corresponding adducts were isolated in moderate to good yields (50–81%) and *ee*s up to 90%. Regarding Grignard reagents, (*R*)-tolBINAP **L107** was the most efficient ligand, affording moderate to excellent *ee*s (55–92%) despite lower 1,4 selectivities (85:15 in the best case).



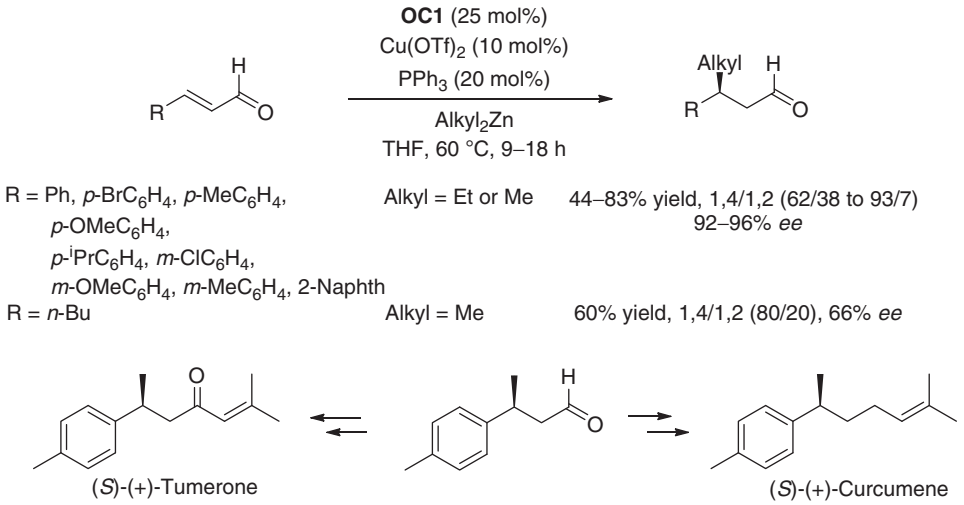
Scheme 77 First copper-catalyzed 1,4-addition of organometallic reagents to challenging α,β-unsaturated enals.

Based on these promising results, Alexakis and Quintard proposed a one-pot sequential Cu-catalyzed 1,4-addition/organocatalyzed α-substitution of enals involving dialkylzincs/vinyl sulfones as nucleophiles/electrophiles to lead to various enantioenriched α,β-functionalized aldehydes and derivatives (Scheme 78).[233] Using (*R*) or (*S*)-BINAP **L108**/CuTC and the organocatalyst **OC1**, excellent enantioselectivities (typically 99%) were obtained for the predominately formed *syn* isomers with good isolated yields (58–74%), whereas no diastereocontrol occurred without any amine catalyst. Similar high selectivities (99% *ee*) were also observed for the sequential Michael/fluorination and chlorination involving **OC2** or **OC3** organocatalysts, respectively. Finally, this methodology was applied to the enantioselective synthesis of (*2S,3S*)-valnoctamide.



Scheme 78 One-pot sequential asymmetric Cu-catalyzed 1,4-addition/organocatalyzed α-substitution of enals.

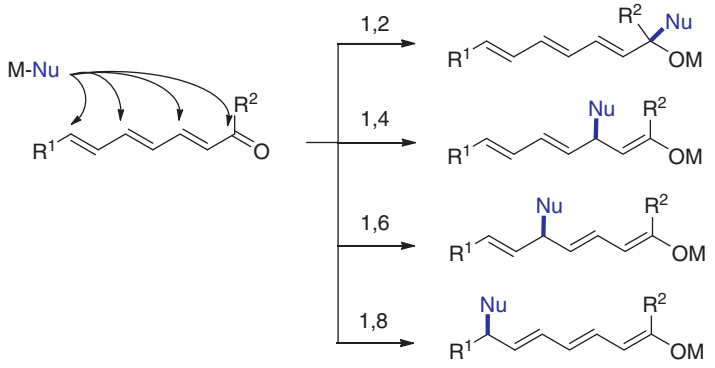
In 2011, another kind of cocatalyzed enantioselective β-alkylation of enals combining copper- and amino- catalysis was reported by Cordova and coworkers (Scheme 79).[234] By using a catalytic mixture of $Cu(OTf)_2$/**OC1**/PPh_3, excellent enantioselectivities were generally observed for the addition of dimethyl and diethylzinc (up to 96%) with a low to good 1,4/1,2 ratio (51/49–98/2). This efficient cocatalytic protocol was applied to the total enantioselective synthesis of bisabolane sesquiterpernes.



Scheme 79 Cocatalyzed enantioselective β-alkylation of enals.

4.04.2.5 Extended Michael Acceptors

Several research groups focused their attention to the copper-conjugate addition involving the more challenging polyenic Michael acceptors.[235] However, the extension of the conjugated system implies solving the problematic regio-control of the nucleophilic attack toward the three electrophilic positions (at least), which coexist in the substrate. Despite the copper-based catalysts being typically 1,4- regioselective, the 1,6- as well as 1,8-position, etc., may also react leading to an undesired mixture of adducts (Scheme 80).

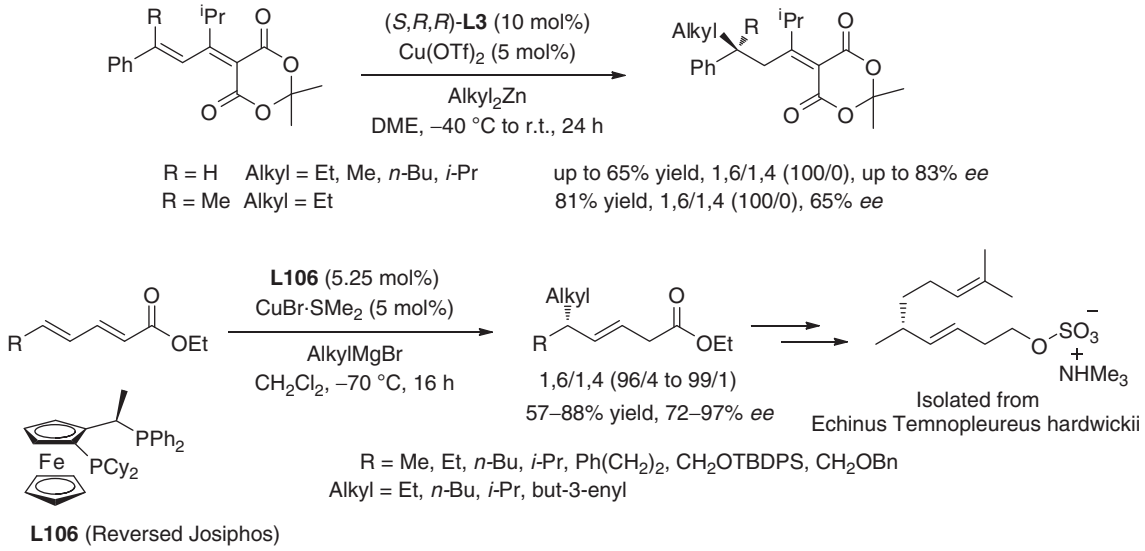


Scheme 80 Regioselectivity with extended Michael acceptors.

Historically, the first (achiral) attempt was introduced by Naef et al. in 1972 with the stoichiometric 1,6-conjugate addition of Gilman cuprate nBu$_2$CuLi to the pentadienic ethyl ester.[236] In 1982, Yamamoto reported that the 1,4/1,6 selectivity was closely dependent on the nature of the cuprate reagent.[237] Indeed, Yamamoto's cuprate (nBuCu · BF$_3$) afforded mainly the 1,4-adduct, whereas the Gilman reagent delivered exclusively the 1,6-adduct. Based on these pioneering works, several studies dealing with cuprates[238] and also application in total (racemic) synthesis[239] were then reported. However, the first enantioselective copper-catalytic version was disclosed in 2001 by the Alexakis group with the addition of diethylzinc to acyclic dienone affording exclusively the 1,6-adduct but with low enantioselectivity of 35%.[240] Therefore, the control of both regio- and enantioselectivity for this kind of Michael acceptor remains an important challenge in the copper-catalyzed ACA. During the last decade, important contributions were achieved in this direction and several efficient asymmetric 1,6- or 1,4-addition of organometallic reagents were reported involving a wide range of extended Michael acceptors such as cyclic and acyclic dieneones, trienones, enynones, dienoic acid derivatives, nitrodienes, and nitroenynes.

4.04.2.5.1 Dienoic acid derivatives

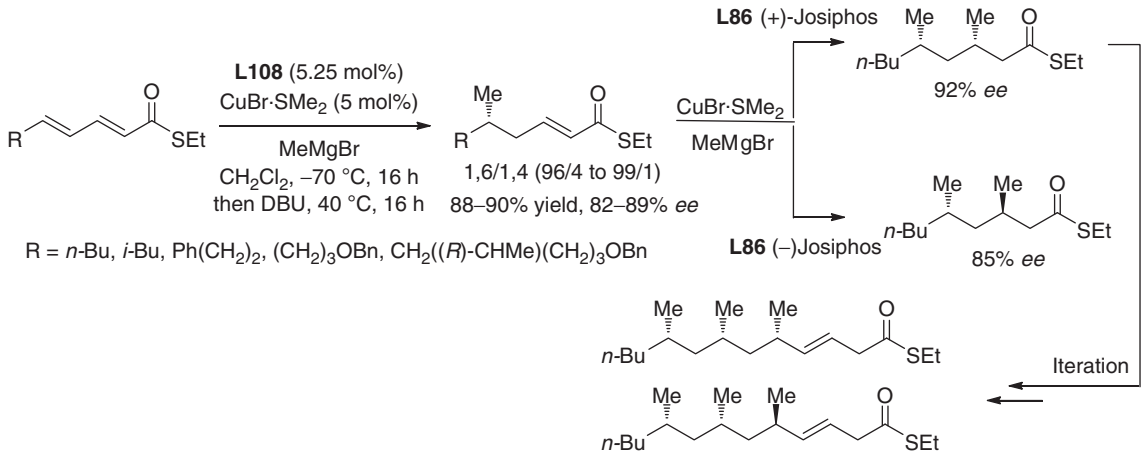
In 2006, Fillion et al. disclosed a remarkable 1,6-regioselective addition of various dialkylzincs to dienic Meldrum's acid derivatives promoted by copper(II)triflate and phosphoramidite (*S*,*R*,*R*)-**L3** (Scheme 81).[241] The creation of both tertiary and quaternary stereogenic centers was accomplished with good or moderate *ee*s (up to 83% and 65%, respectively). According to these



Scheme 81 1,6-Cu ACA involving dienic Meldrum's acid derivatives and dienoates.

pioneering results in this area, Feringa and coworkers proposed to study the addition of Grignard reagents to various dienoates (Scheme 81).[242] Interestingly, the ferrocene-based ligand **L106** (reversed Josiphos) enabled to reach high levels of 1,6 versus 1,4 regioselectivity (up to 99:1) in combination with moderate to good isolated yields (57–88%) and excellent *ee*s (72–97%), except for Me-, Ph-, and *i*Bu-MgBr reagents because of their low reactivity. This methodology was then applied to the synthesis of a natural sulfated alkene.

In 2010, Feringa and coworkers extended their methodology to dienic thioester derivatives (Scheme 82).[243] Advantageously, the valuable MeMgBr could be successfully introduced with good 1,6-selectivities (85/15 to 99/1), yields (78–88%), and enantioselectivities (82–89%) for a wide range of substrates. After reconjugation of the corresponding enantioenriched 1,6-adducts under basic condition, the resulting α,β-unsaturated thioester was then reengaged in a subsequent 1,4-Cu-ACA giving the desired *anti* or *syn* adducts in 85–92% *ee*s. Moreover, thanks to the thioester function, an iterative strategy afforded a powerful synthetic route to highly desirable enantioenriched 1,3-deoxypropionate moieties.

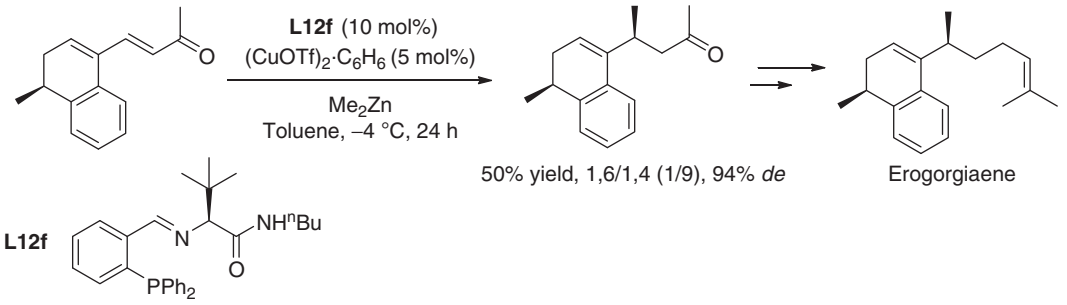


Scheme 82 Iterative sequential 1,6/1,4 Cu-ACA for the enantioselective synthesis of 1,3-deoxypropionate units.

4.04.2.5.2 Dienones, trienones, and enynones

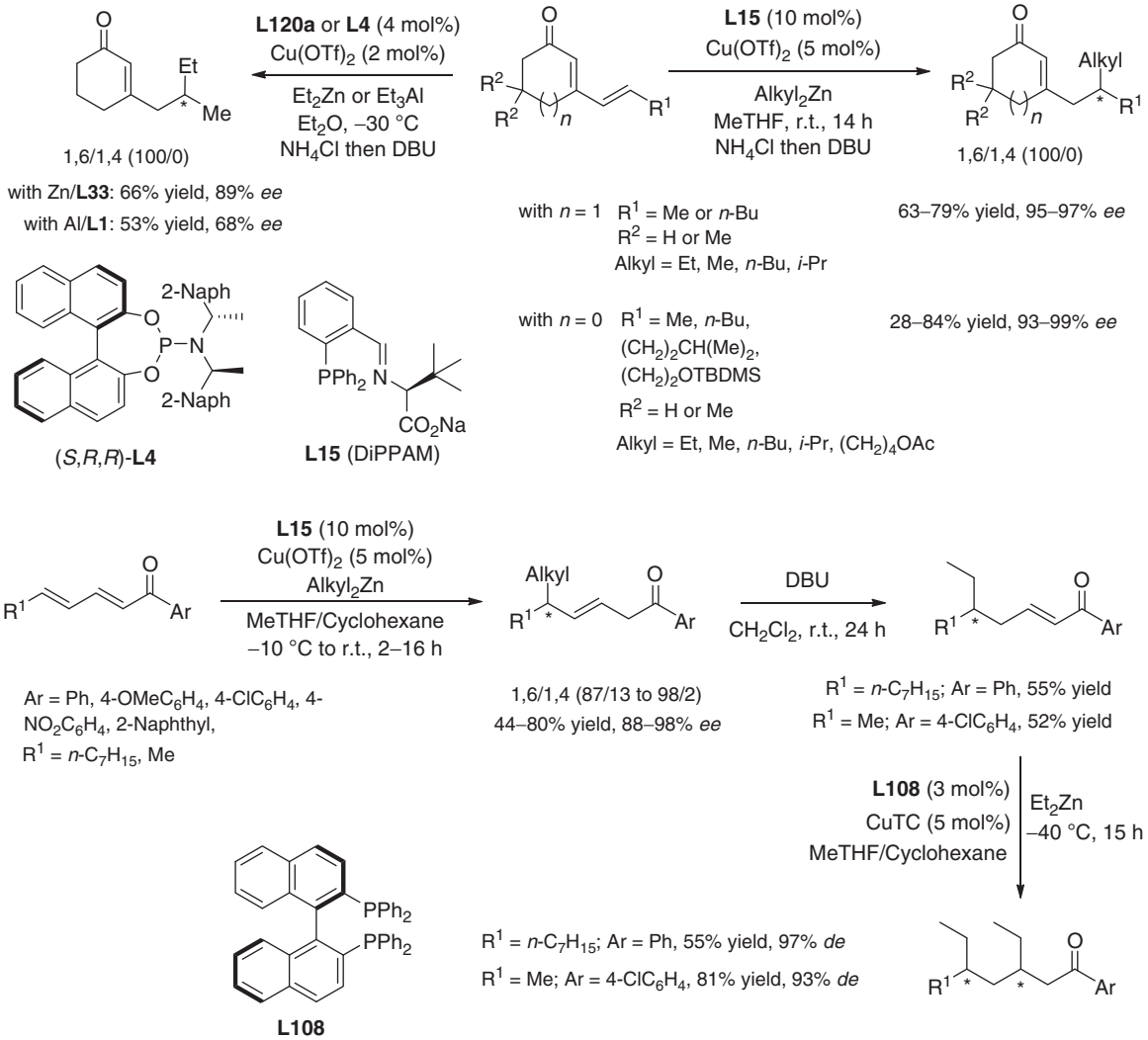
The first report dealing with an enantioselective 1,4-addition of an organozinc reagent to a dienone Michael acceptor was disclosed by Hoveyda and coworkers during the total asymmetric synthesis of erogorgiaene in 2004 (Scheme 83).[244] The reaction of dimethylzinc in the presence of small-peptide ligand **L12f** and copper(I)-triflate afforded predominantly the corresponding 1,4-adduct in 50% yield and an excellent diastereoselectivity of 94%.

Later, Alexakis and Mauduit reported the 1,6-addition of both diethylzinc and triethylaluminum nucleophiles to cyclic dienones catalyzed by phosphoramidites **L120a**/**L4** in the presence of copper(II)triflate (Scheme 84).[245] The 1,6-adducts were



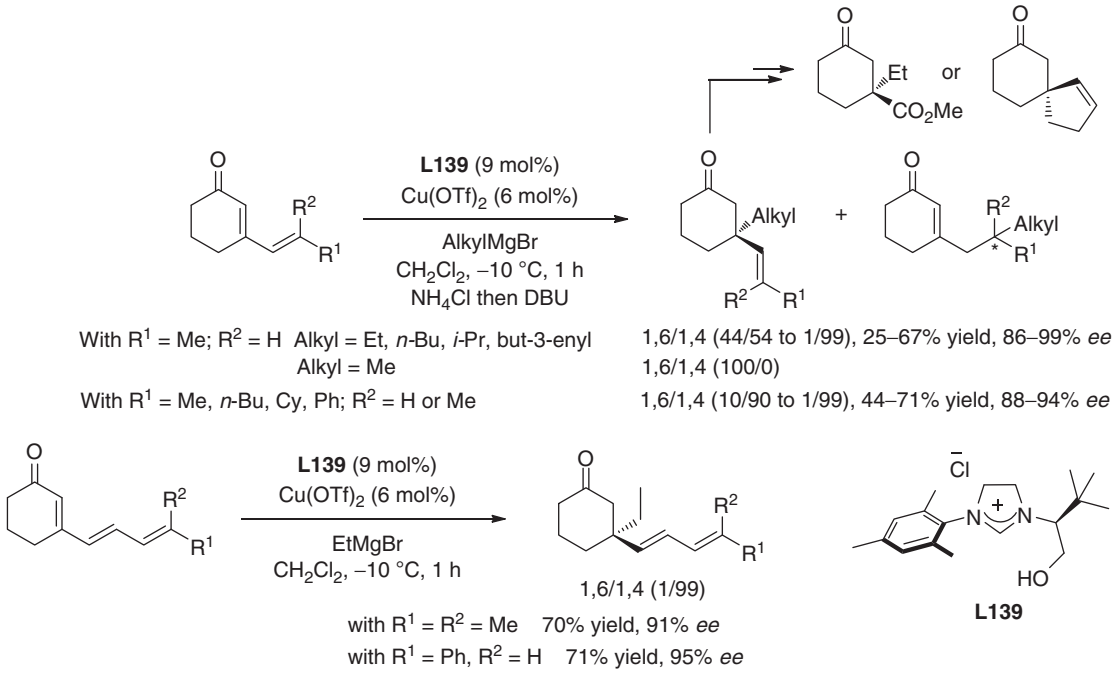
Scheme 83 First Cu–ACA involving a dienone Michael acceptor.

exclusively formed with *ee*s ranging from 68% to 89%. In 2010, the enantioselectivities were significantly improved by employing the carboxylate-phosphino Schiff-based ligand **L15** (DiPPAM), allowing reaching *ee*s up to 97%.[246] The scope was then extended to various dialkylzinc reagents and five-membered ring dienones with similar high 1,6-enantioselectivities (93–99%). However, both developed catalytic systems were less enantioselective regarding bicyclic systems (40–68%). Recently, this methodology was successfully extended to more challenging acyclic α-aryldienones, leading to 1,6-adducts in excellent regio- (up to 98/2) and enantioselectivities (88–98% *ee*).[247] Moreover, after the isomerization of the double bond, the resulting α,β-unsaturated enone was then reengaged in the 1,4-conjugate addition of diethylzinc catalyzed by CuTC in the presence of the (*R*)-binap **L108** (Scheme 84). Moderate to good yields (53–81%) were reached with excellent diastereoselectivities (93–97%).



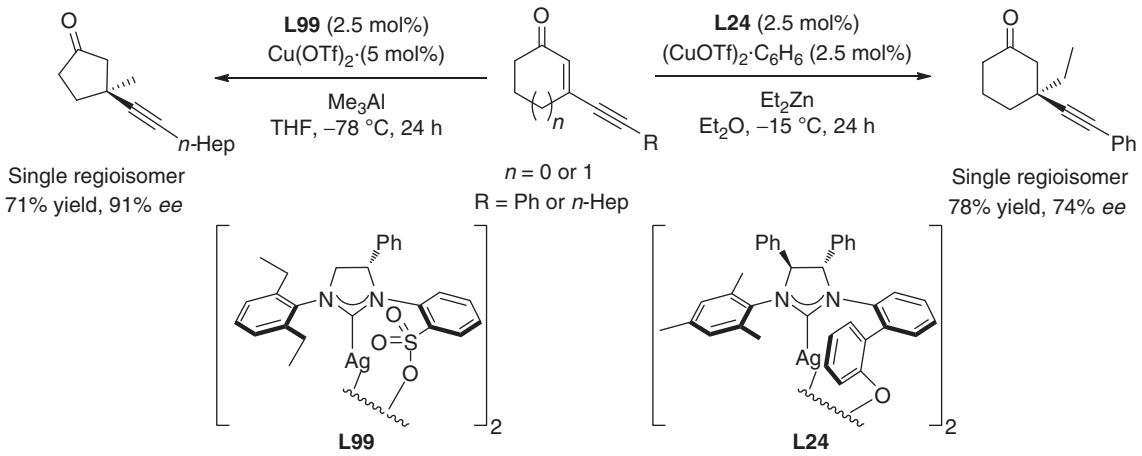
Scheme 84 Phosporamidite and DiPPAM ligands for 1,6-ACA on cyclic dienones.

The same authors reported in 2008 an unusual 1,4-selectivity for the addition of Grignard reagents to cyclic or bicyclic dienoes when the reaction was catalyzed by hydroxyalkyl-NHC ligand **L139** and $Cu(OTf)_2$ (Scheme 85).[245] This 1,4-selectivity was quite surprising as the most substituted position was preferably attacked by the hard nucleophile, leading to the formation of quaternary stereogenic centers. Nevertheless, the authors highlighted that the hydroxyIalkyl-chelating function was necessary to get this 1,4-regioselectivity. Various Grignard reagents were successfully introduced affording the desired 1,4-adducts with excellent regio- (up to 98%) and enantioselectivities (up to 99%). Advantageously, alkene units could be converted to carboxylic acid esters or spirocyclic moiety. This methodology was then extended to the addition of EtMgBr to trienones providing a single 1,4-regioisomer with *ee*s ranging from 91% to 95%. Nevertheless, in the case of MeMgBr, a mixture of three regioisomers was observed with 80% *ee* for the expected 1,4-adduct, a key intermediate in the total synthesis of riccardiphenol B.[248]



Scheme 85 Formation of enantioenriched quaternary centers through the 1,4-ACA of Grignard reagents to cyclic dienones and trienones.

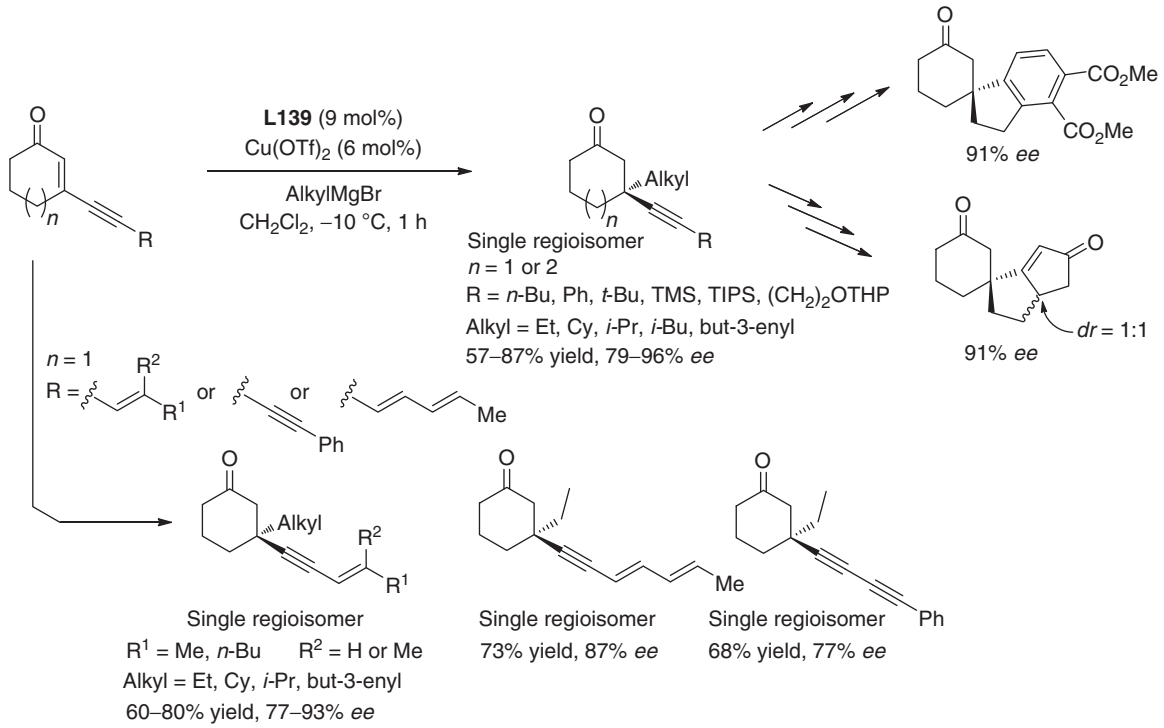
In the case of enynone Michael acceptors, the first example of Cu-ACA was reported by Hoveyda and coworkers. By using phenoxy-chelating NHC-Ag complex **L24** in the presence of copper(I)triflate, a perfect 1,4 selectivity occurred for the addition of diethylzinc to the hexacyclic enynone, giving the corresponding all-carbon quaternary stereogenic center adduct in 78% of yield and 74% *ee* (Scheme 86).[249] Similar 1,4-selectivity and 91% *ee* were reached during the ACA of trimethylaluminum reagent to five-membered cyclic enynone catalyzed by sulfonated-NHC Ag complex **L99**/$Cu(OTf)_2$.[130] It is important to highlight that these



Scheme 86 The first 1,4-ACA of organometallic nucleophiles to cyclic enynones.

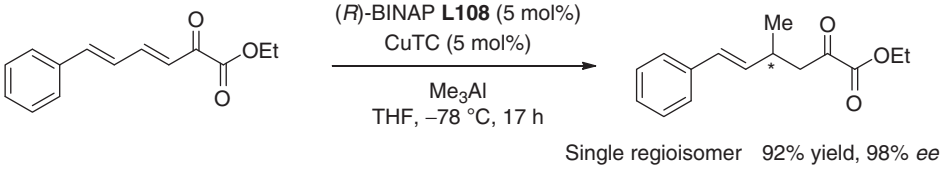
1,4-regioselectivities were contrary to that reported by Krause who observed predominantly 1,6-adducts from the addition of cuprate nucleophiles.

In 2011, Alexakis and Mauduit proposed to extend the scope of their hydroxy-chelating NHC **L139**/copper-based catalytic system to cyclic enynones (Scheme 87).[250] The addition of Grignard reagents afforded also exclusively 1,4-adducts with good yields and excellent *ee*s (up to 96%). Interestingly, the alkyne moiety was converted into valuable building blocks without any alteration of enantioselectivity. Finally, this methodology was then successfully applied to polyconjugated systems leading to the exclusive formation of all-carbon quaternary centers with good yields and excellent enantioselectivities, reaching up to 93% *ee*.[248]



Scheme 87 1,4-ACA of Grignard reagents to cyclic enynones and polyconjugated derivatives.

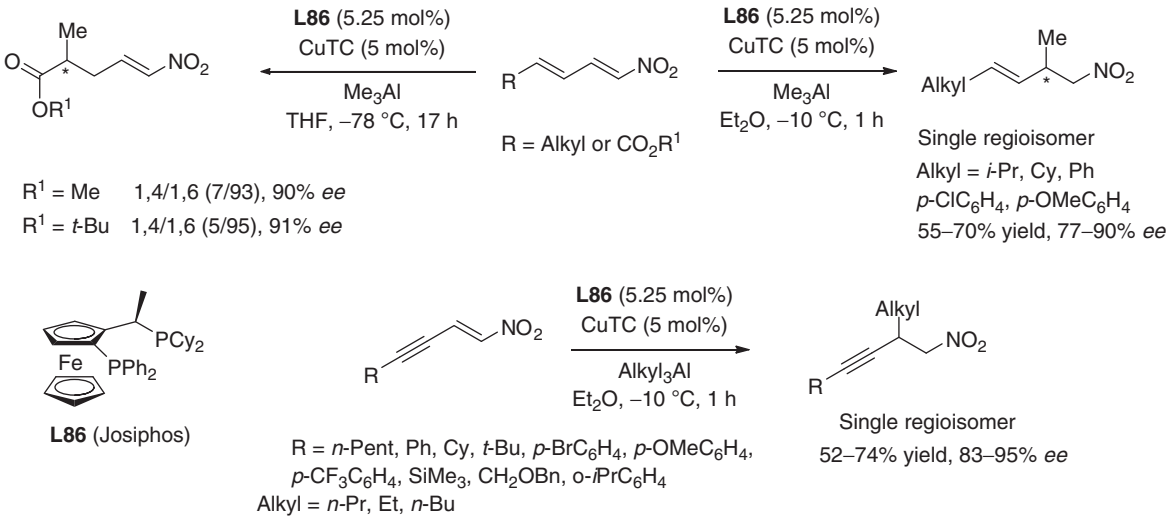
Only one example was described with a dienone bearing an ester function in α-position (Scheme 88).[148] Alexakis and Gremaud observed the exclusive formation of the 1,4-adduct with a remarkable *ee* of 98% for the Cu-ACA of trimethylaluminum to the dienic α-ketoester catalyzed by the (*R*)-BINAP **L108**/CuTC.



Scheme 88 1,4-ACA of aluminate reagents to a dienic α-ketoester.

4.04.2.5.3 Nitroenynes, nitrodienes, and nitrodienoates

The first report on Cu-ACA involving $\alpha,\beta,\delta,\gamma$-unsaturated nitroolefines was disclosed by the Alexakis group in 2010 (Scheme 89).[251] By using the well-known Josiphos ligand **L86** in the presence of copper-thiophene carboxylate, a full 1,4-selectivity occurred for the addition of trialkylaluminum reagents to nitroenymes. The valuable enantioenriched adducts (up to 95% *ee*) were isolated in good yields. The same catalytic system also afforded exclusively 1,4-methylated adducts in the case of nitrodienes with *ee*s reaching up to 90%. However, when nitrodienoates were involved, the regioselectivity switched in favor of the 1,6-adducts with 91% of enantioselectivity.



Scheme 89 1,4- and 1,6-ACA of aluminate reagents to nitroenynes, nitrodienes, and nitrodienoates.

4.04.3 Rh/Ir/Ru Metal-Catalyzed ECA

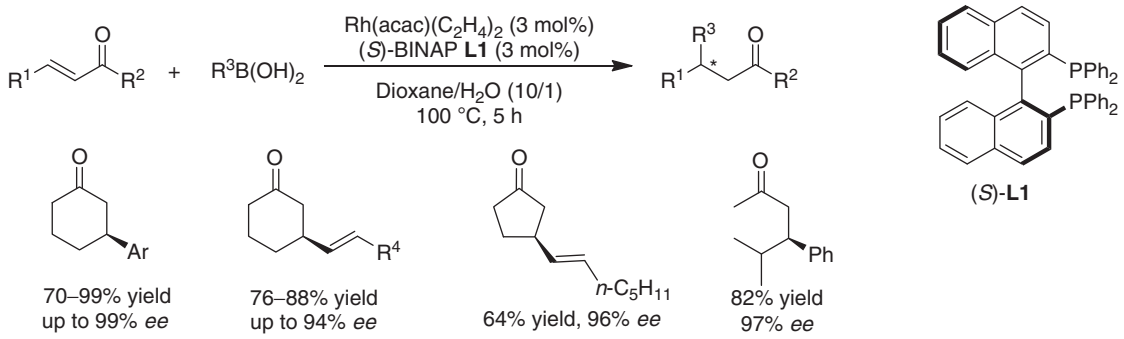
4.04.3.1 Rh-Catalyzed ACA

During the last decade, asymmetric rhodium-catalyzed conjugate addition reactions, with organometallic reagents (B, Si, Zn, Zr, Al, and Ti) to activated alkenes,[252] have received great attention and have become a relevant synthetic tool for the synthesis of complex molecules and intermediates in fine chemistry.[253]

4.04.3.1.1 α,β-Unsaturated enones

4.04.3.1.1.1 Addition of boronic acid reagents

In 1998, Hayashi and coworkers[254] described the first rhodium-promoted ACA of aryl- and alkenylboronic acids to various cyclic and acyclic enones (Scheme 90), using (*S*)-BINAP (**L1**) as chiral ligand, with high *ee* values. The mechanism[255] and the optimization of the reaction conditions[254,256] have been fully investigated in the last decade. To improve this powerful synthetic methodology for the preparation of optically active *β*-aryl-substituted ketones, Lukin et al.[257] have recently developed a highly practical protocol, using an *in situ*-generated Miyaura-type catalyst.

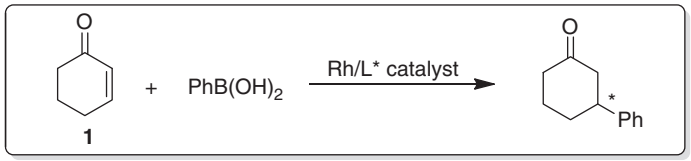


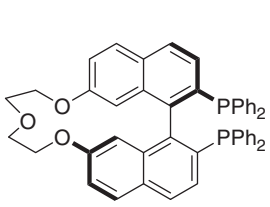
Scheme 90 Pioneering ACA reaction of aryl- and alkenyl-boron reagents to unsaturated ketones.

Since these pioneering results, intense research works on Rh-promoted ACA reactions on cyclic and linear enones have been carried out, with the design of a plethora of new enantiopure ligands. In this paragraph, a nonexhaustive overview of various ligands, which were successfully used in the asymmetric 1,4-addition of arylboronic acids to *α,β*-unsaturated cyclic ketones, and more particularly on cyclohex-2-enone **1**, a model substrate, will be described. It is noteworthy that some ligands might be better suited for specific substrates.

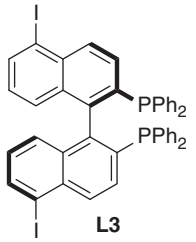
First, other bidentate phosphorus ligands have been evaluated in the conjugate addition of phenylboronic acid to cyclohex-2-enone **1** (Scheme 91). Optically active BINAP analogs, such as 7,7′-disubstituted BINAPs **L2**[258] or 5,5′-diiodoBINAP **L3**,[259] or C2-symmetric bisphosphines such as the diphonane ligand **L4**,[260] as well as BINOL-based diphosphinites or bisphosphoramidites (**L5** or **L6**),[261,262] were successfully applied with good to excellent enantioselectivity (90–99.6% *ee*). In general, axially chiral ligands

proved their efficiency in terms of catalytic activity and enantiodiscrimination (up to 99% *ee*), as for instance (*S*)-P-phos **L7**,[263] the electron-poor (*S*)-MeOBiphep derivatives **L8** and **L9**,[264] the heterotopic atropoisomeric diphosphines (**L10**, **L11**),[265] and recently the SYNPHOS analogs (**L12**, **L13**).[266] Remarkably, the Rh/MeO-F_{12}-Biphep **L9** catalyst was applicable to a gram-scale asymmetric 1,4-addition of arylboron reagent to cyclohex-2-enone **an1** with a turnover number (TON) of 320 000 and a 98% *ee*.[264b] The cyrhetrene **L14**, bearing a planar chirality, proved also to be a promising candidate.[267] Two original catalytic systems were also developed in aqueous media: the water-soluble BINAP-based ligand (**L15**)[268] catalyzed the ACA reaction in ethylene glycol with a

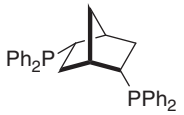




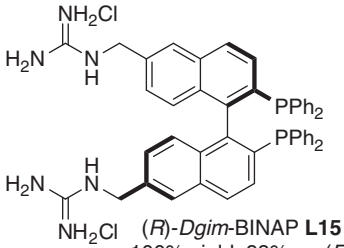
L2
99% yield, 97% *ee* (*R*)



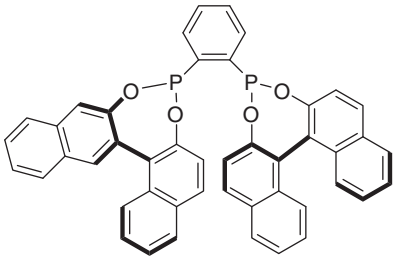
L3
97% yield, 97.9% *ee* (*R*)



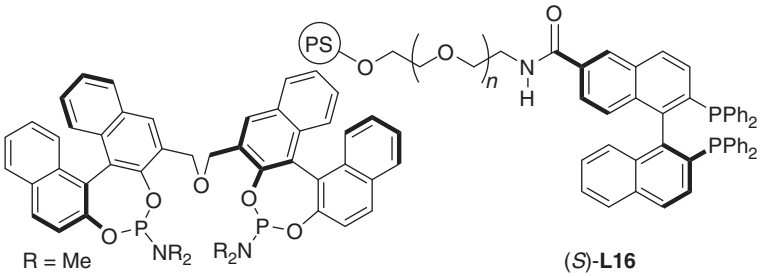
(2*S*,5*S*)-Diphonane **L4**
83% yield, 90% *ee* (*R*)



(*R*)-*Dgim*-BINAP **L15**
100% yield, 98% *ee* (*R*)
(ethylene glycol)

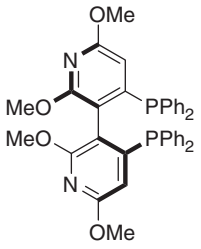


(*R*,*R*)-**L5**
100% yield, 99% *ee* (*S*)

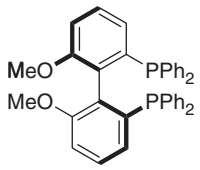


(*R*,*R*)-**L6**
99% yield, 99.6% *ee* (*R*)

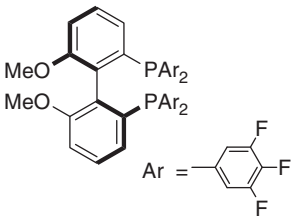
(*S*)-**L16**
83% yield, 97% *ee* (*S*)
(water)



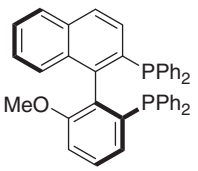
(*S*)-P-Phos **L7**
> 99% yield, 99% *ee*



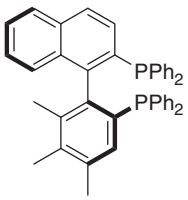
(*S*)-MeO-Biphep **L8**
97% yield, 98% *ee* (*S*)



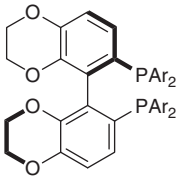
(*R*)-MeO-F_{12}-Biphep **L9**
99% yield, >99% *ee* (*R*)

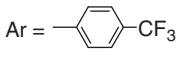


(*S*)-MeO-NAPhePHOS **L10**
95% yield, 98% *ee* (*S*)

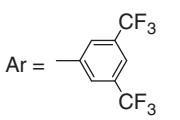


(*R*)-TRiMe-NAPhePHOS **L11**
95% yield, 98% *ee* (*S*)

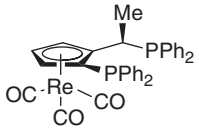




(*R*)-p-CF_3-SYNPHOS **L12**
92% yield, 99% *ee* (*R*)



(*R*)-3,5-di-CF_3-SYNPHOS **L13**
95% yield, 99% *ee* (*R*)

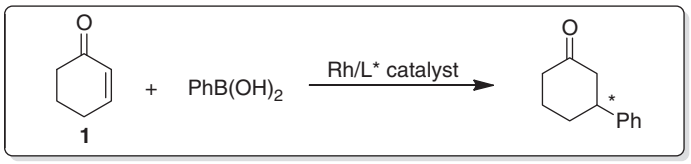


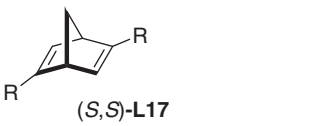
(*R*, *Sp*)-**L14**
93% yield, 95% *ee* (*R*)

Scheme 91 Relevant chiral bidentate phosphorus ligands for 1,4-addition to cyclohexen-2-one.

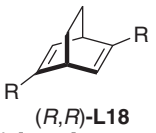
TON of 13 200 and an amphiphilic resin-supported BINAP ligand (**L16**)[269] was prepared and used for the 1,4-conjugate addition in water with high enantiodiscrimination and with an efficient catalyst recycling.

Secondly, enantiopure diene ligands are also ideally suited for the ACA reaction with outstanding results (Scheme 92).[270] Since the first application of chiral diene ligand **L17b** in the 1,4-addition of arylboronic acids to cyclohex-2-enone **1**,[271] various mono- or di-substituted bicyclic diene scaffolds,[272] as well as chiral chain dienes (**L26** and **L27**),[273] were successfully used with great selectivity. Remarkably, the water-soluble chiral diene ligand **L23** gave high asymmetric induction in neat water. The relevant features of the rhodium/diene tandem rely on high catalytic activities and selectivities (e.g., 0.005–0.01 mol% of Rh/L catalyst could catalyze ACA reactions with high yields and enantioselectivities with TOF up to 14 000 h^{-1}).[274]

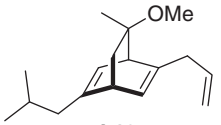




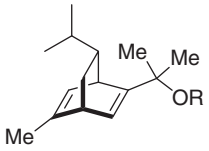
(*S*,*S*)-**L17**
(Bicyclo[2.2.1]hepta-2,5-diene)
L17a R = Me 90% yield, 95% *ee* (*S*)
L17b R = Bn 87% yield, 96% *ee* (*S*)
L17c R = Ph 89% yield, 97% *ee* (*S*)



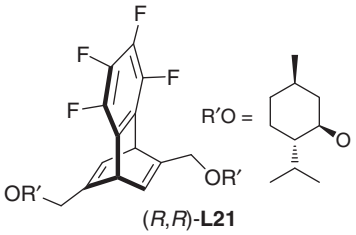
(*R*,*R*)-**L18**
(Bicyclo[2.2.2]octa-2,5-diene)
L18a R = Ph 97% yield, 96% *ee* (*R*)
L18b R = Bn 97% yield, 95% *ee* (*R*)



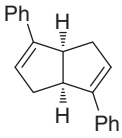
L19
87% yield, 95% *ee* (*S*)



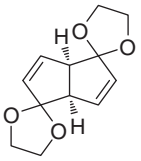
(*R*,*R*,*R*)-**L20**
L20a R = H 90% yield, 99.3% *ee* (*R*)
L20b R = Me 90% yield, 99.1% *ee* (*R*)



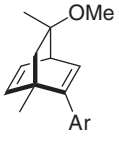
(*R*,*R*)-**L21**
98% yield, 99% *ee* (*R*)



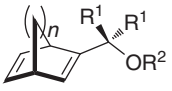
(3a*S*,6a*S*)-**L22**
(Bicyclo[3.3.0]octa-2,5-diene)
74% yield, 95% *ee* (*R*)



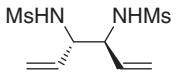
L23
94% yield, 93% *ee* (*S*)
(H_2O)



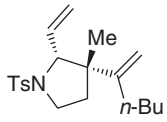
(*S*,*R*,*R*)-**L24**
>99% yield, 98% *ee* (*S*)
Ar = 2,6-$(Me)_2C_6H_3$



L25
n = 0, R^1 = Me, R^2 = BOM 95% yield, 96% *ee* (*R*)
n = 1, R^1 = Me, R^2 = H >98% yield, 95% *ee* (*R*)
n = 1, R^1 = *i*-Bu, R^2 = BOM >98% yield, 96% *ee* (*R*)



(*S*,*S*)-**L26**
96% yield, 95% *ee* (*R*)

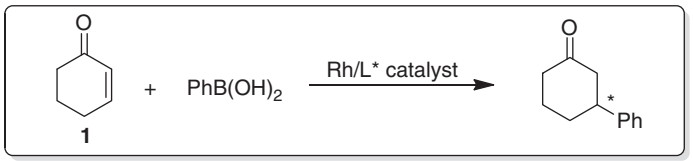


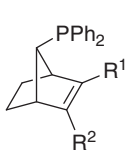
L27
89% yield, 97% *ee* (*S*)

Scheme 92 Pertinent enantiopure diene ligands for 1,4-addition to cyclohexen-2-one.

Based on the fact that phosphines are more coordinating ligands toward rhodium than olefins but that the latter could provide an ideal chiral environment around the metallic center, phosphane-olefin hybrids[275] proved to be highly effective for this reaction with good activities and selectivities (Scheme 93). The olefin part of the ligand is assumed to be a crucial parameter toward the catalyst's activity.

Monodentate chiral ligands are also promising candidates for the Rh-promoted ACA reaction (Scheme 94). The BINOL-based phosphoramidite **L33** was particularly efficient for this 1,4-addition, associated with its easy preparation and structural flexibility.[276] Andrus and coworkers[277] reported the use of highly tunable monodentate NHCs **L34**. Recently, a 'combinatorial transition-metal catalysis' approach was applied to this transformation, through the heterocombination of tropos monodentate phosphoramidite ligands **L35** and **L36**.[278] Tomioka and coworkers[279] described an L-proline-derived amidomonophosphine **L37**, which behaves as a hemilabile ligand with a phosphorus atom that strongly bonds to Rh(I) and a coordinatively labile oxygen.

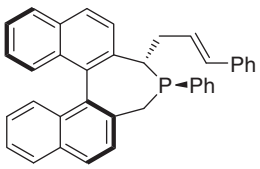




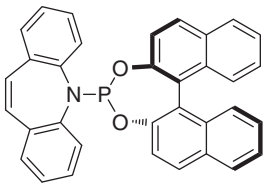
L28

R^1 = Ph, R^2 = H 98% yield, 93% *ee* (*R*)

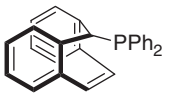
R^1 = H, R^2 = Ph 94% yield, 93% *ee* (*R*)



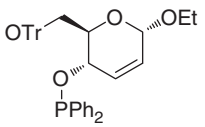
(S,Sa,Sp)-**L29**
88% yield, 98% *ee* (*S*)



(*S*)-**L30**
90% yield, 92% *ee* (*R*)

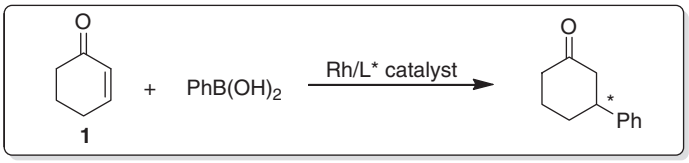


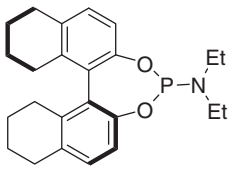
(*R*)-**L31**
85% yield, 95% *ee* (*R*)



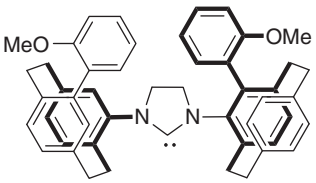
Gluco-enoPhos **L32**
80% yield, 99% *ee* (*R*)

Scheme 93 Pertinent phosphane-olefin hybrid ligands for 1,4-addition to cyclohexen-2-one.

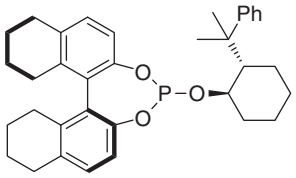




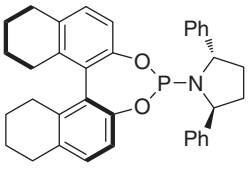
(*S*)-**L33**
86% yield, 99% *ee* (*S*)



(Sp)-**L34**
96% yield, 98% *ee* (*S*)

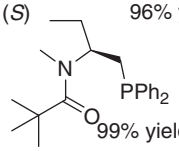


L35
100% yield, 70% *ee* (*R*)



L36
100% yield, 36% *ee* (*R*)

L35 + L36
100% yield, 95% *ee* (*R*)

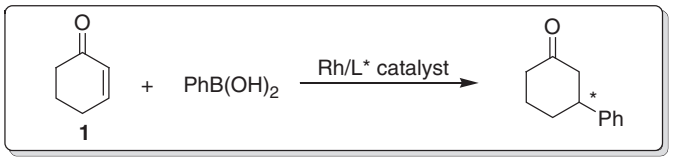


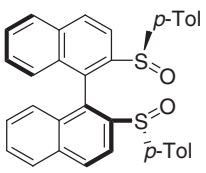
L37
99% yield, 97% *ee* (*S*)

Scheme 94 Monodentate ligands for 1,4-addition to cyclohexen-2-one.

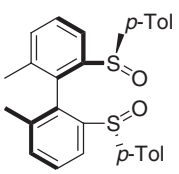
Recently, various sulfoxide ligands have emerged as a remarkable class for the enantioselective Rh-promoted 1,4-addition (Scheme 95). Dorta and coworkers[280] reported chiral bis-sulfoxides **L38** and **L39** as outstanding ligands for the addition of arylboronic acids over various cyclic α,β-unsaturated ketones, achieving a near-perfect asymmetric induction. Their unparalleled selectivity was attributed to an unusual electronic recognition between the sulfoxide moieties and the prochiral substrate, while allowing the use of low catalyst loadings and stoichiometric amounts of expensive boronic acids. Liao and coworkers described a readily prepared C_2-symmetric chiral bis-sulfoxide **L40**,[281] as well as a novel class of chiral hybrid P-SO ligands **L41**,[282] using a *tert*-butylsulfinyl moiety as the ligating entity and chiral source with excellent results. Recently, a new family of easily synthesized and stable chiral sulfoxide-olefin ligands (**L42**, **L43**, **L44**) showed pertinent results in terms of activities and selectivities.[283] Interestingly, the ligands **L42** and **L43** afforded a completely switchable stereoselectivity thanks to the olefin geometry (branched vs. linear). Simple *N*-sulfinyl-based optically active sulfur-olefin ligands **L44** also proved to be active and selective under mild conditions.[284]

This survey gives an overview of the ligand families used in the 1,4-addition of phenylboronic acid to cyclohexen-2-one **1**, a benchmark reaction. Obviously, this reaction is tolerant of a wide range of organoboron reagents as well as cyclic enones and

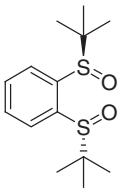




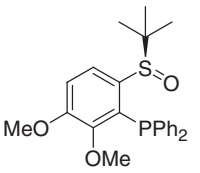
(*P*, *R*, *R*)-*p*-tol-BINASO **L38**
99% yield, 98% *ee* (*S*)



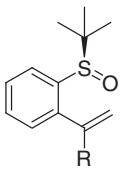
(*P*, *R*, *R*)-*p*-tol-Me-Bipheso **L39**
98% yield, > 99% *ee* (*R*)



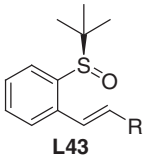
(*R*, *R*)-**L40**
96% yield, 98% *ee* (*R*)



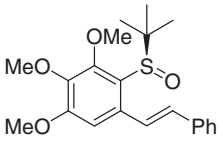
L41
99% yield, 98% *ee* (*R*)



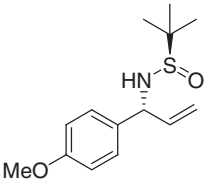
L42
L42a R = CH_3 98% yield, > 99% *ee* (*R*)
L42b R = Ph 98% yield, 95% *ee* (*R*)



L43
L43a R = CH_3 93% yield, 98% *ee* (*S*)
L43b R = Ph 97% yield, 97% *ee* (*S*)



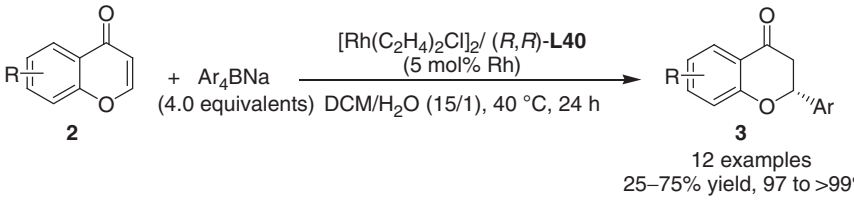
L44
99% yield, 97% *ee* (*R*)

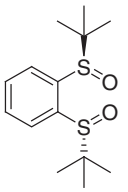


L45
90% yield, 94% *ee* (*R*)

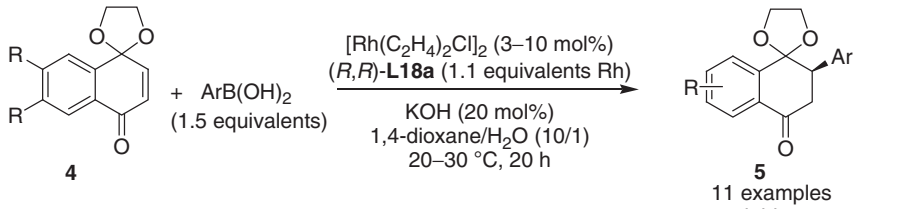
Scheme 95 Sulfoxides as a promising new class of ligands for 1,4-addition to cyclohexen-2-one.

could be successfully performed at the multigram scale with high catalyst turnover. Interestingly, this methodology was applied to the synthesis of some biologically interesting molecules (Scheme 96), thus showing its broad scale on more sophisticated cyclic α,β-unsaturated ketones. The conjugate addition to the challenging chromenones **2** enables to access optically pure flavanones **3** in

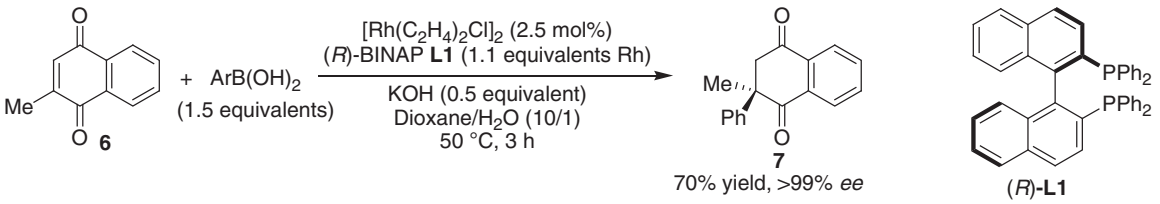




(*R*, *R*)-**L40**



(*R*,*R*)-**L18a**
(*R*,*R*)-Ph-bod*

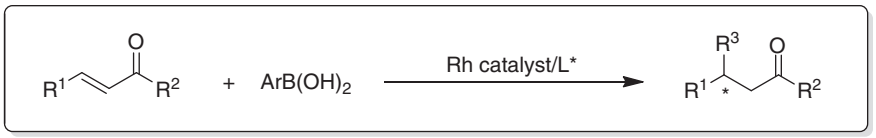


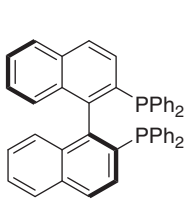
(*R*)-**L1**

Scheme 96 ACA reaction to more sophisticated cyclic enones toward the synthesis of biological molecules.

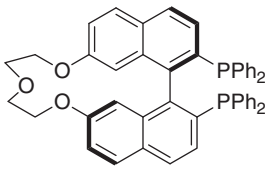
the presence of bis-sulfoxide **L40** as chiral ligand,[281] with high yields, thanks to the use of sodium tetraarylborates. In parallel, a novel synthetic approach to 2-aryltetralones **5** was developed through the 1,4-addition of aryl- or alkenylboronic acids to naphthoquinone monoketals **4**, catalyzed by a Rh/chiral diene system.[285] Quinone-based substrates, such as 2-methyl-1,4-naphthoquinone **6**,[286] were also used as acceptors, leading to the formation of quaternary carbon stereocenters with good yields and high enantioselectivity.

In some cases, the reaction scope of the previously described catalysts has been further extended to linear enones (e.g., **8** or **9**), but the examples are relatively scarce compared to cyclic ones. The most pertinent catalytic systems are given in **Scheme 97**. Similar diphosphine ligands, such as BINAP **L1**[287] and its derivative **L2**,[258] bipyridyl-based diphosphine **L7**,[263] heterotopic atropisomeric diphosphines (**L8**, **L10**, **L11**)[265] and SYNPHOS derivatives **L13**[266] were successfully used on linear enones **8** and **9** with good *ee* values (> to 90%). Chiral diene ligands, based on a bicyclo heptadiene (**L17b**) or [2.2.2]octadiene (**L18**, **L20**, **L21**, **L41**)

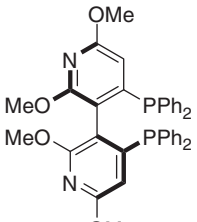




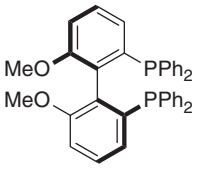
(*S*)-Binap
L1



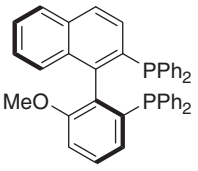
L2



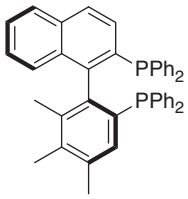
(*S*)-P-Phos **L7**



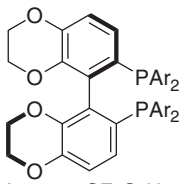
(*S*)-MeO-Biphep
L8



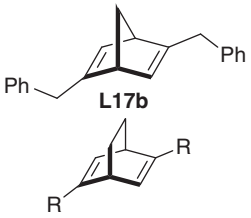
(*S*)-MeO-NAPhePHOS
L10



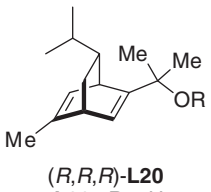
(*R*)-TRiMe-NAPhePHOS
L11



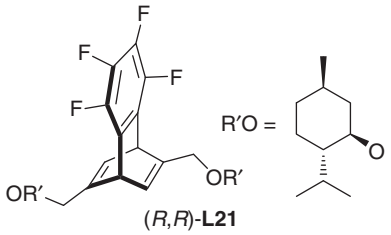
Ar = 3,5-$CF_3C_6H_3$
(*R*)-3,5-di-CF_3-SYNPHOS
L13



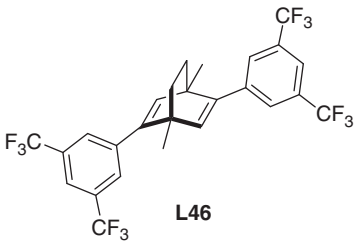
(*R*,*R*)-**L18**
L18b R = Bn



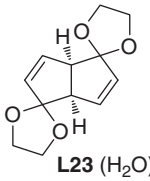
(*R*,*R*,*R*)-**L20**
L20a R = H
L20b R = Me



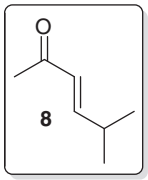
(*R*,*R*)-**L21**



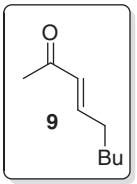
L46



L23 (H_2O)
14 examples
82–92% yield, 73–98% *ee*
R^1 = Me, Ph, R^2 = *n*-Pr, *i*-Pr, Ph



Ligand	Yield (%)	*ee* (%)
L1	82	97
L2	88	97
L7	90	90
L13	76	97
L17b	81	97
L18	97	94
L20a	84	96

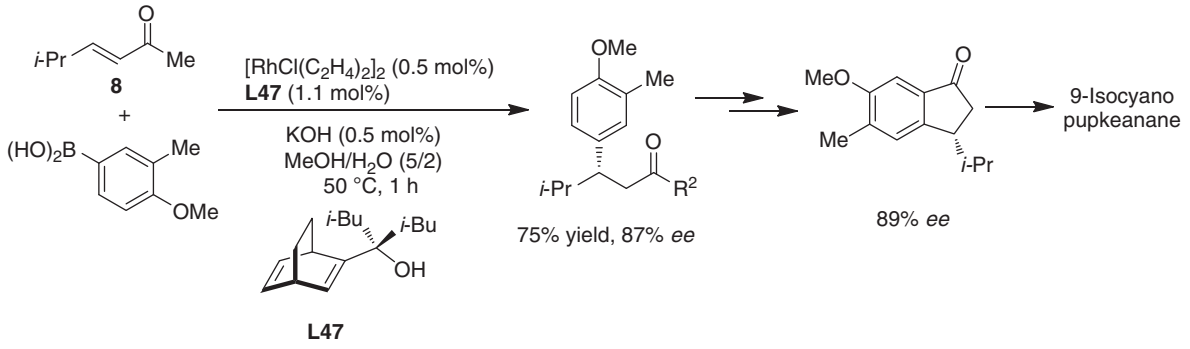


Ligand	Yield (%)	*ee* (%)	Ligand	Yield (%)	*ee* (%)
L1	88	92	**L21**	85	99
L7	86	96	**L17b**	84	95
L8	87	98	**L18**	94	98
L10	88	97	**L20a**	95	98.8
L11	87	96	**L20b**	90	99
L13	92	93	**L46**	99	97

Scheme 97 ACA reaction to linear enones: some most pertinent catalytic systems.

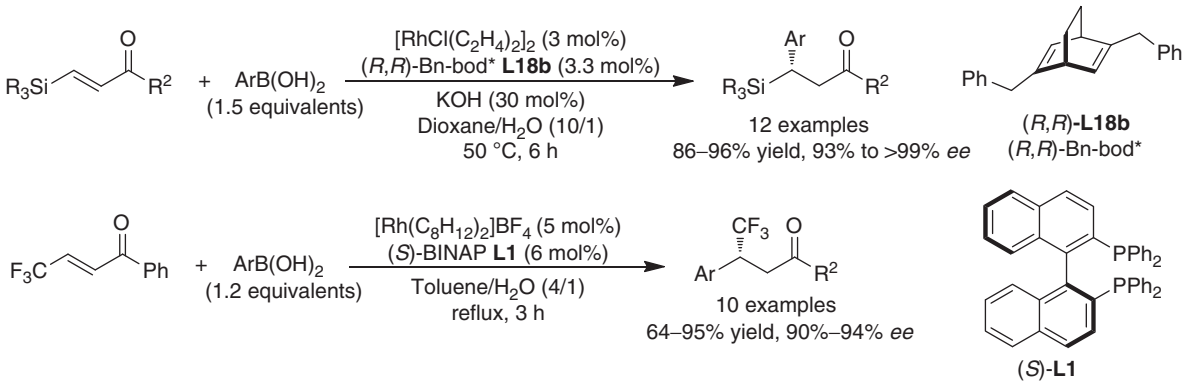
skeleton,[271,272b,d,g,288] also proved their high efficiency in the 1,4-addition to acyclic unsaturated ketones. Recently, a robust predictive structure–property relationship (QSPR) model for enantioselectivity was proposed by Carnell and coworkers,[289] showing that more electron-deficient diene ligands are better candidates for promising enantiodiscrimination and that electronic effects are more pivotal than steric ones. Interestingly, the 1,4-addition to various α,β-unsaturated linear enones was successfully performed at room temperature in neat water using a hydrophilic bicyclo[3.3.0] diene ligand **L23** to afford the 1,4-adducts in good yields and very high enantioselectivities.[290]

The ACA reaction on enone **8** proved to be particularly interesting for the synthesis of a key intermediate in the preparation of 9-isocyanopupkeanane,[272f] using a new enantiopure bicyclooctadiene-based ligand **L47** and a very low Rh loading (Scheme 98).



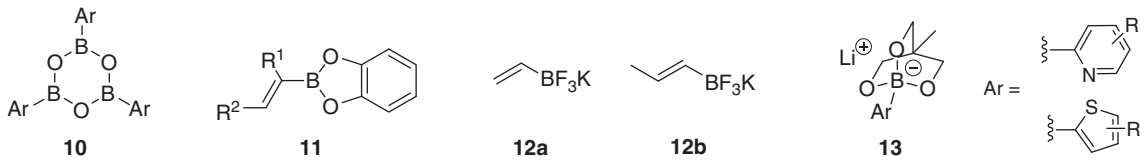
Scheme 98 Enantioselective synthesis of 9-isocyanopupkeanane.

Moreover, the 1,4-addition reaction is not limited to simple α,β-unsaturated ketones. β-Silyl-α,β-enones showed their potential as acceptors in the Rh-mediated ACA reaction of organoboron reagents, in the presence of the chiral diene ligand **L18b**, thus leading to the formation of optically enriched organosilanes, which could further be transformed to β-hydroxyketones by Tamao–Fleming oxidation (Scheme 99).[291] Likewise, treatment of fluoroalkylated electron-deficient olefins with various boronic acids in the presence of Rh(I) coordinated with (*S*)-BINAP **L1** (Scheme 10-AN), provided products of particular interest in the medicinal, pharmaceutical, and agricultural sectors.[292]



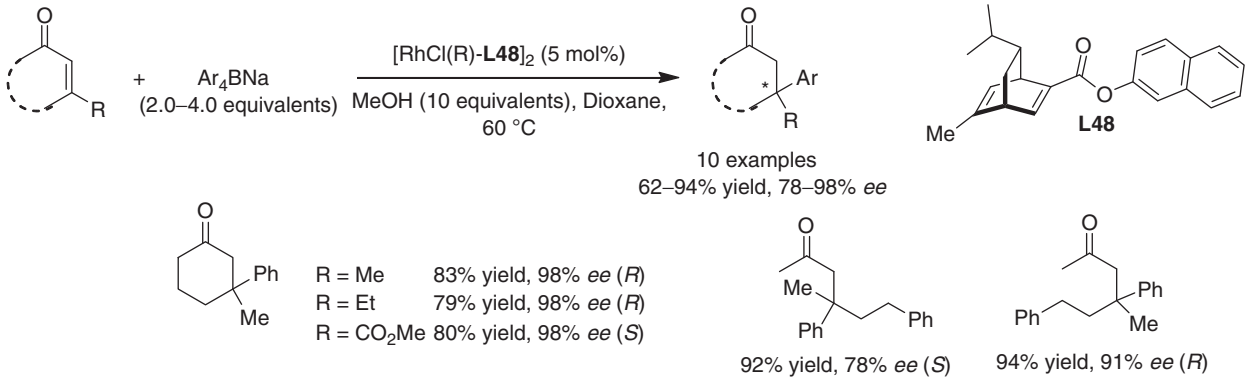
Scheme 99 ACA of arylboronic acids to β-silyl-α,β-enones and to fluoroalkylated electron-deficient olefins.

Parallel to the use of arylboronic acids, other nucleophiles, such as arylboroxines **10** (Scheme 100), proved their usefulness.[293] They enable to perform the addition of the organoboron reagent with a precise stoichiometry owing to their higher stability. Sodium tetraarylborates were also successfully used for the generation of quaternary carbon stereocenters on β,β-disubstituted α,β-unsaturated ketones with the chiral diene **L48** (Scheme 101).[294] Although the Rh-catalyzed ACA reaction with aryl-boronic acids

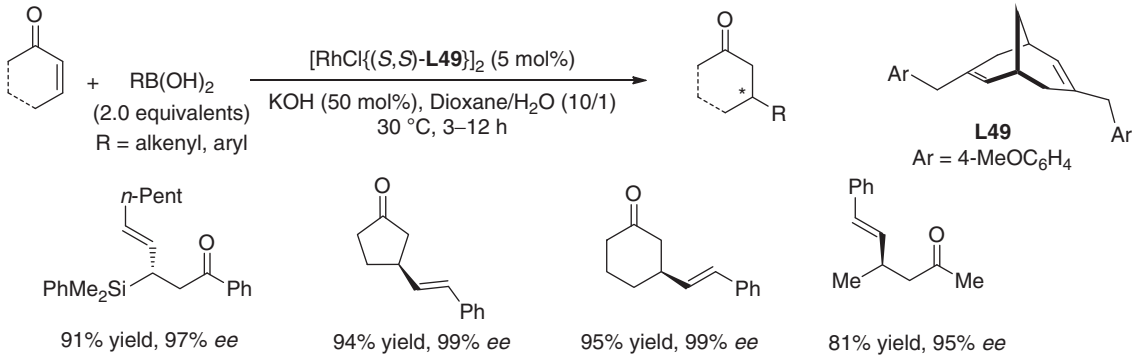


Scheme 100 Alternative aryl-, alkenyl- or heteroaryl- boron reagents.

has been well explored, the addition of alkenyl nucleophiles to Michael acceptors proved to be more challenging, particularly owing to the low stability of these nucleophiles. However, some synthetic strategies have been developed over the last decade, using alkenyl organometallic reagents (Scheme 100).[295] Thus, alkenylcatecholboranes **11**, prepared *in situ* by hydroboration of alkynes with catecholboranes, are good alkenylating reagents.[287] This versatile method is one of the most practical routes to introduce a broad range of *E*-alkenyl nucleophiles. Potassium trifluoroborates, which present a greater stability than boronic acids, are particularly attractive, because very small nucleophiles (such as vinyl- and propenyltrifluoroborates, respectively **12a** and **12b**) could be prepared.[285,296] Interestingly, Hayashi and coworkers[297] prepared novel C_2-symmetric chiral diene ligands **L49**, possessing a 3,7-disubstituted bicyclo[3.3.1] nona-2,6-diene skeleton, as efficient ligands for the 1,4-addition of alkenyl- as well as aryl-boronic acids to various enones (Scheme 102). Recently, lithium heteroaryl(triol)borates **13** (Scheme 100) used for the conjugate additions of electron-deficient heteroaryl groups to α,β-unsaturated carbonyl compounds afforded the 1,4-adducts with high enantioselectivities in the presence of a Rh(I) catalyst chelated with a chiral BINAP or BIPAM ligand.[298]



Scheme 101 Formation of quaternary carbon stereocenters through ACA reaction.



Scheme 102 Asymmetric 1,4-addition of alkenylboron reagents to α,β-unsaturated ketones.

4.04.3.1.1.2 Addition of miscellaneous nucleophiles

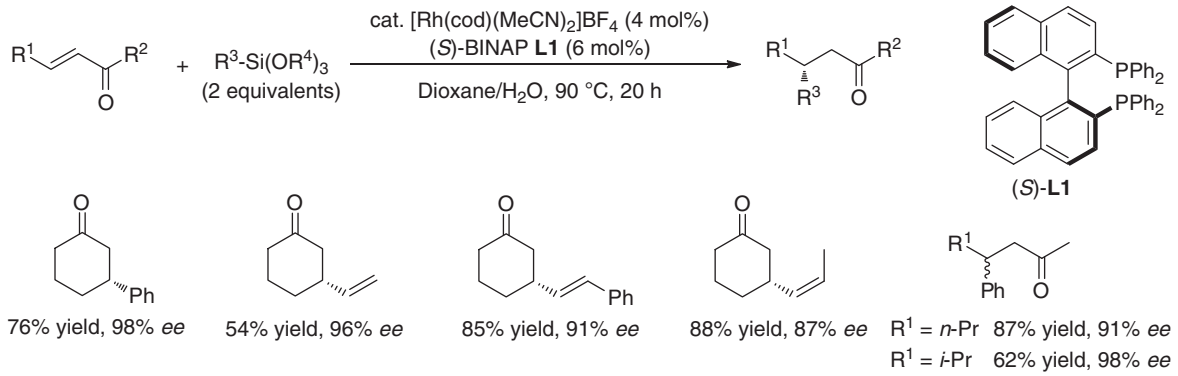
Although organoboron derivatives have been widely used for the Rh-mediated ACA reaction, alternative organometallic reagents have also been developed, including silicon, zirconium, aluminum, zinc as well as titanium derivatives.

4.04.3.1.1.2.1 Silicon nucleophiles

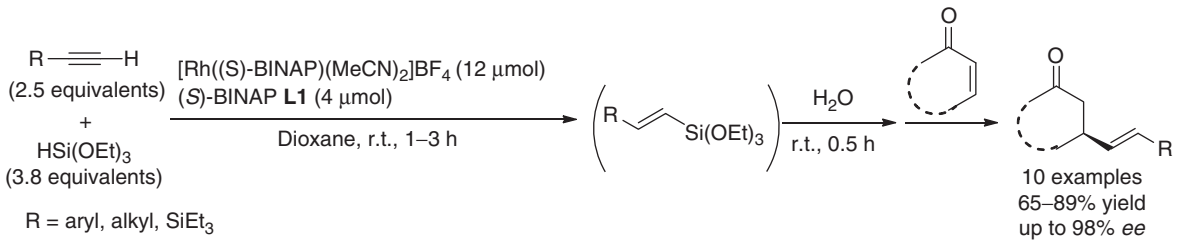
Organosilicon reagents are particularly relevant owing to their low cost, low toxicity, and their easy handling. Inoue and coworkers[299] first reported the highly enantioselective 1,4-addition of organosiloxanes to α,β-enones by a chiral rhodium complex generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP **L1** (Scheme 103). This approach allows to introduce aryl and both (*E*)- or (*Z*)-alkenyl groups.

Considering that the hydrosilylation of 1-alkynes with triethoxysilane could be catalyzed by a rhodium complex $[Rh((S)\text{-BINAP})(MeCN)_2]BF_4$, Hayashi and Otomaru[300] developed a tandem one-pot Rh-promoted hydrosilylation-ACA reaction (Scheme 104). The *E*-alkenylsilanes, obtained by hydrosilylation of terminal alkynes, were then subjected to the addition onto cyclic α,β-unsaturated ketones to afford the 1,4-addition products with other 90% *ee*.

However, these silicon organyls are very sensitive toward acids, bases, and moisture. Thus, Nakao et al.[301] proposed a new family of stable and reusable tetraorganosilicon reagents (alkenyl-, aryl-, silyl-dimethylsilanes) that undergo Rh-promoted

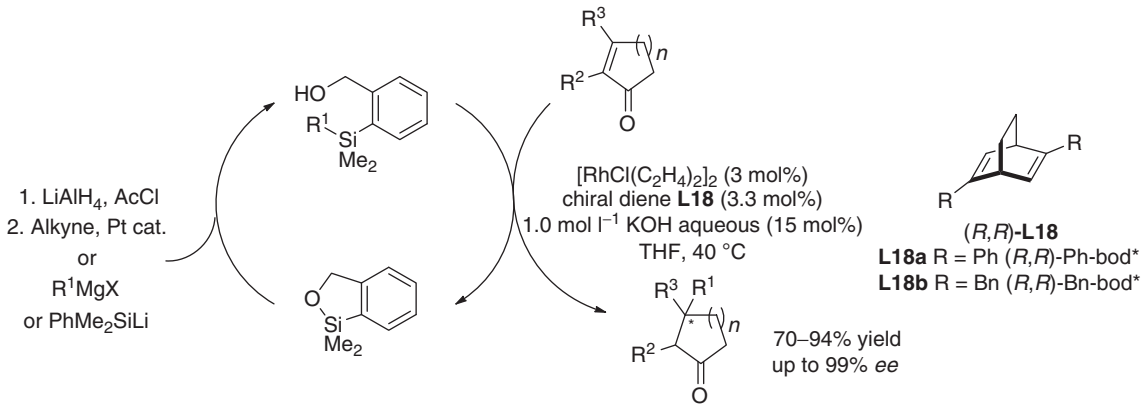


Scheme 103 Rh-catalyzed asymmetric 1,4-addition of organosiloxanes to α,β-enones.

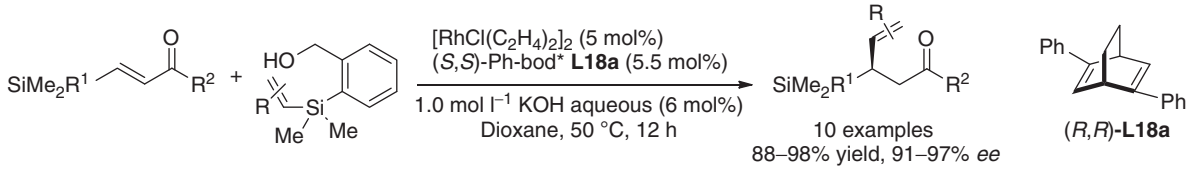


Scheme 104 Tandem one-pot Rh-promoted hydrosilylation-ACA procedure.

1,4-additions to various α,β-unsaturated carbonyl acceptors (cyclic and acyclic enones, amides, piperidinones) under mild conditions in the presence of chiral diene ligands **L18** (Scheme 105). This methodology was successfully extended to β-silyl-α,β-unsaturated ketones (Scheme 106).[302]

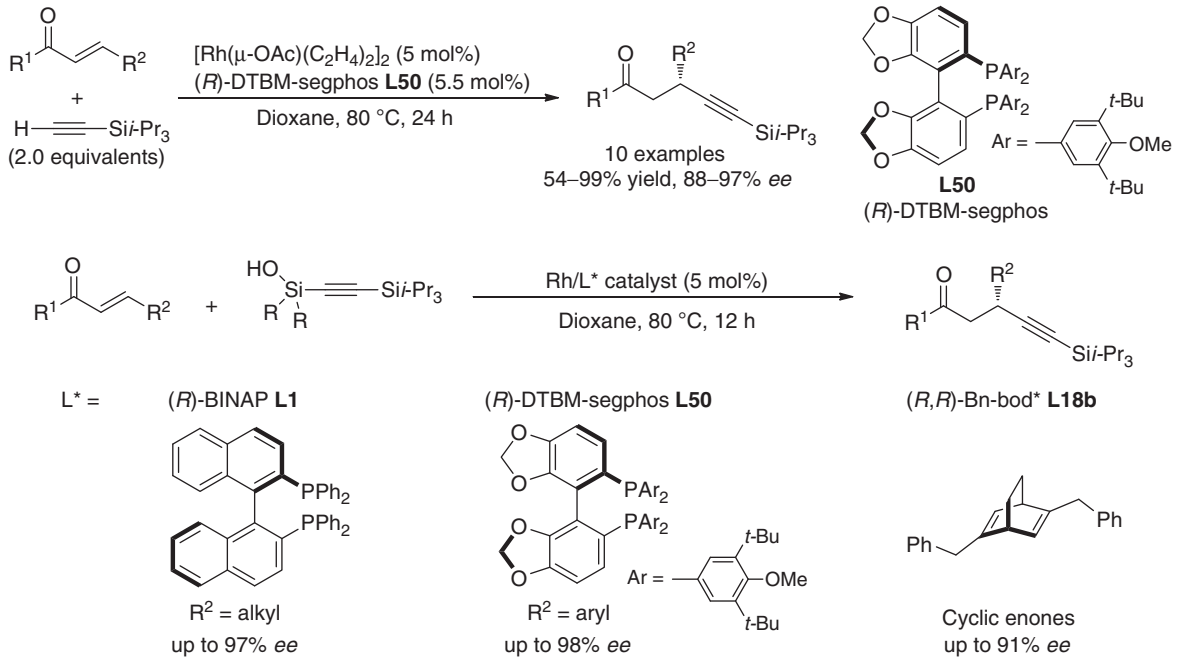


Scheme 105 Organo[2-(hydroxymethyl)phenyl]dimethylsilanes as relevant nucleophiles for the Rh-promoted ACA.



Scheme 106 Applications to β-silyl-α,β-unsaturated ketones.

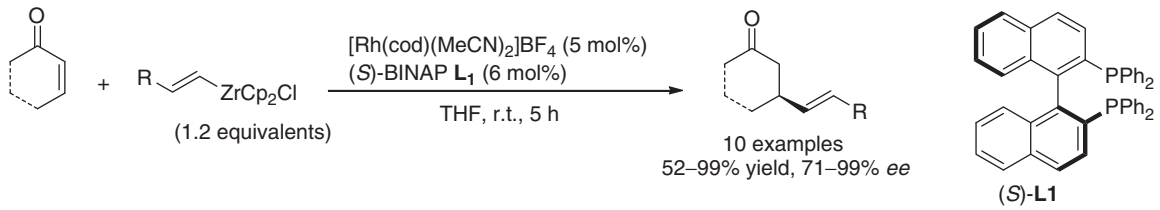
More recently, the ACA of akynyl groups was described through two approaches, either the addition of (triisopropylsilyl) acetylene in the presence of a rhodium/(*R*)-DTBM-segphos **L50** catalyst[303] or (triisopropylsilyl)ethynylsilanols with various chiral rhodium systems according to the nature of the enones (Scheme 107).[304]



Scheme 107 ACA of alkynyl groups to α,β-unsaturated ketones.

4.04.3.1.1.2.2 Zirconium nucleophiles

Alkenylzirconocene chlorides, which were easily prepared by reaction of a terminal alkyne with Schwartz reagent, proved to be pertinent nucleophiles in the ACA reaction to either cyclic and acyclic α,β-enones (Scheme 108), in the presence of a chiral rhodium complex generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP **L1**, with high asymmetric induction (up to 99% *ee*).[305] The presence of a synthetically valuable transient enolate could be interesting for subsequent reactions, as demonstrated by Nicolaou in 2005 for the spirocyclic system of vannusal A.[306]



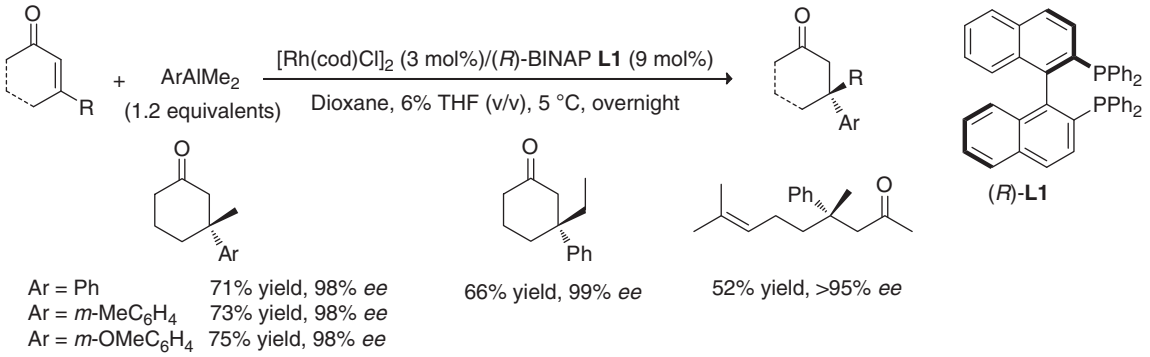
Scheme 108 Asymmetric 1,4-addition of alkenylzirconium reagents to α,β-enones by Rh-BINAP complex.

4.04.3.1.1.2.3 Aluminum nucleophiles

In 2010, Alexakis and coworkers[307] showed that aryl alanes are excellent nucleophiles for the rhodium-catalyzed conjugate addition reaction to both trisubstituted cyclic or acyclic α,β-enones under mild conditions (Scheme 109), with the commercially available BINAP **L1** ligand, thus generating quaternary stereogenic centers with high *ee* values (up to 99% *ee*). A significant electronic effect promoted by the substituent in the 4-position of enones was observed, directing the nucleophilic attacks toward this position despite the steric hindrance.

4.04.3.1.1.2.4 Zinc and titanium nucleophiles

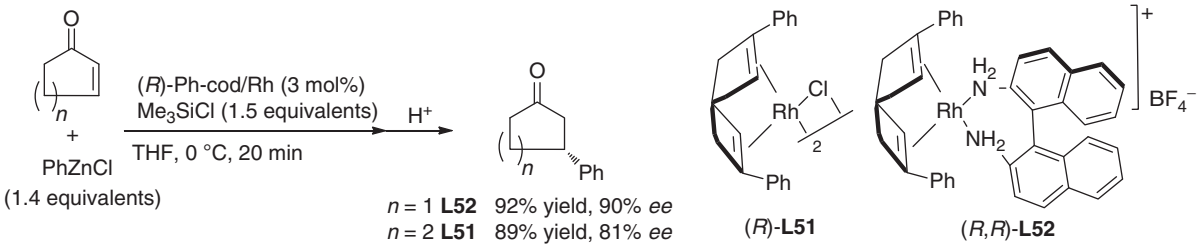
The scope of the nucleophiles suitable for the ACA transformation was also expanded to organotitanium and organozinc derivatives, which are more nucleophilic than their boron counterparts and could be added to α,β-unsaturated compounds at room



Scheme 109 Arylalanes as pertinent nucleophiles for the ACA reaction to trisubstituted enones.

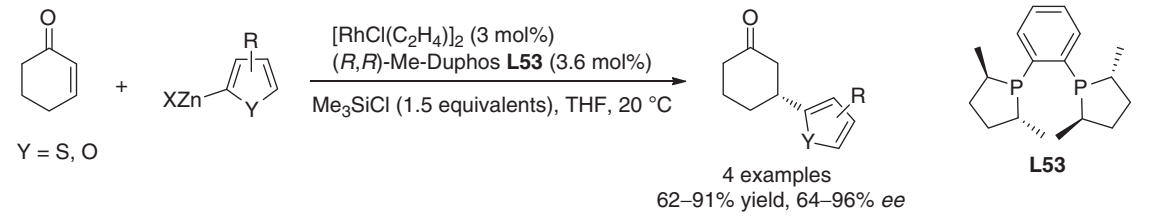
temperature. The reactions are usually performed in aprotic conditions, thus allowing to trap the stable titanium and zinc enolates for further reactions.

Enantiomerically pure rhodium complexes bearing 1,5-diphenyl-1,5-cyclooctadiene as a chiral diene ligand were successfully used in the asymmetric 1,4-addtion of phenylzinc chloride to α,β-unsaturated cyclic ketones in the presence of chlorotrimethylsilane with high catalytic activity and enantioselectivity (Scheme 110).[308]



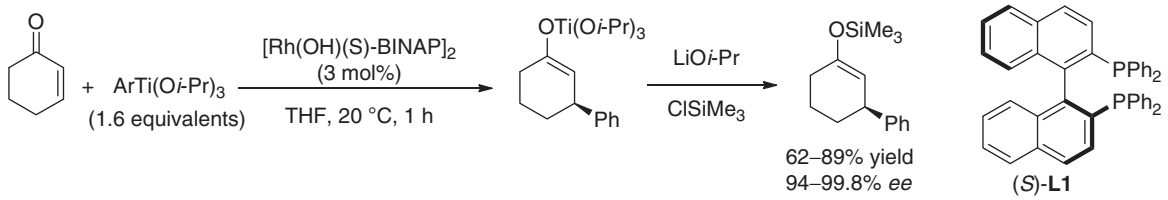
Scheme 110 Rh-promoted asymmetric addition of phenylzinc chloride to cyclic enones.

Recently, 2-heteroaryzinc donors, combined with chlorotrimethylsilane, could also be used in the enantioselective conjugate addition reaction, in the presence of a complex derived from $[Rh(C_2H_4)_2Cl]_2$ and Me-Duphos **L53**,[309] which proved to be superior to established catalysts for this challenging reaction (Scheme 111).



Scheme 111 Rh-mediated ACA reaction of heteroaromatic organozinc reagents to enones.

Similarly, the use of aryltitanium triisopropoxides ($ArTi(O\text{-}i\text{-}Pr)_3$) as arylating reagents for the rhodium-catalyzed asymmetric 1,4-addition in nonprotic solvent leads to the formation of chiral titanium enolates with high enantioselectivity, which could further be transformed into the very useful synthetic intermediates such as silyl enol ethers (Scheme 112).[310]



Scheme 112 Rh-mediated ACA reaction of heteroaromatic organozinc reagents to enones.

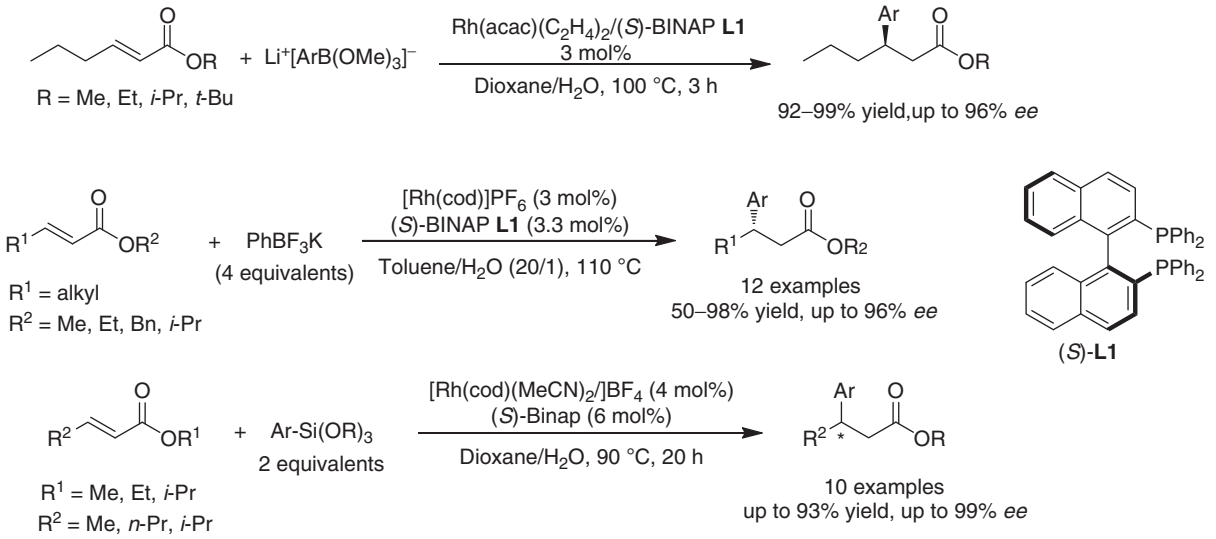
4.04.3.1.2 Ester and lactone substrates

Following the pioneering works on the Rh-mediated ACA onto α,β-unsaturated esters, the method was extended to α,β-unsaturated esters or lactones. Although these substrates are less reactive, they constitute promising acceptors, affording β-substituted esters with high asymmetric induction.

4.04.3.1.2.1 α,β-Unsaturated esters

The Rh-promoted ACA reaction to linear α,β-unsaturated esters proved to be relevant for the synthesis of promising intermediates for the preparation of optically active compounds.

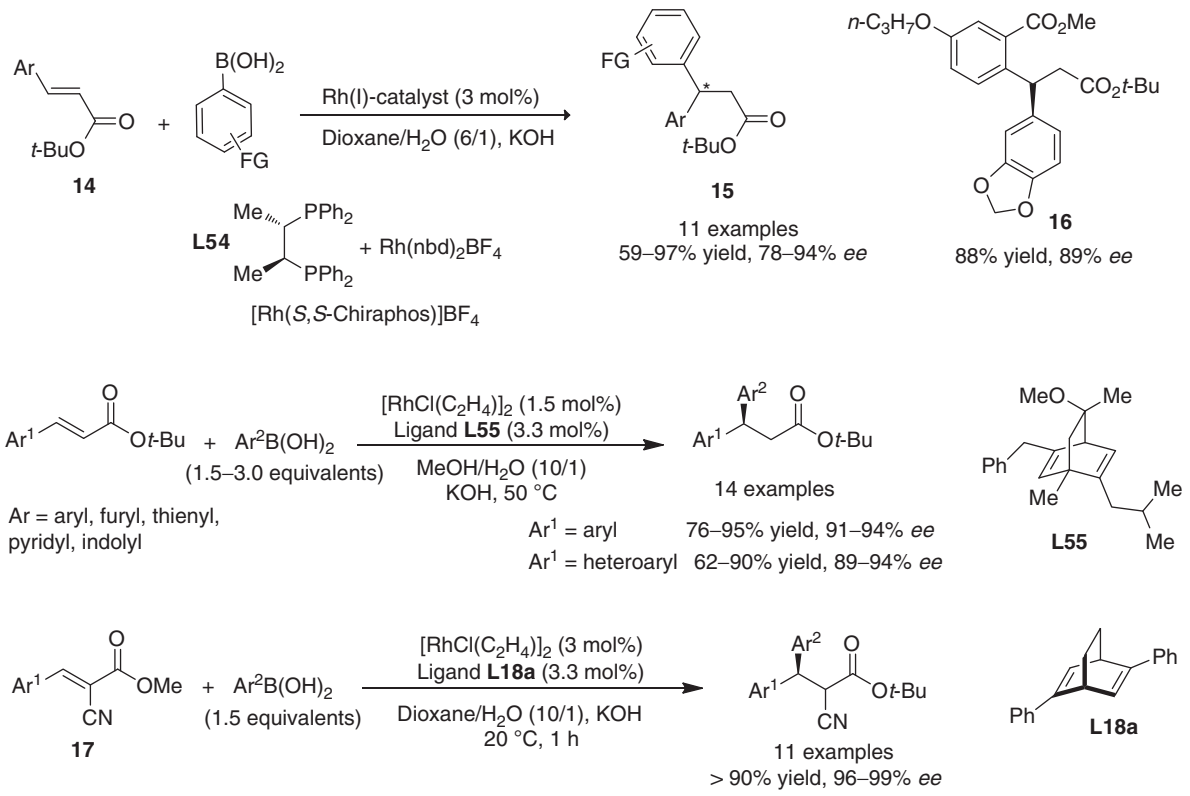
First, both Hayashi[311] and Miyaura[312] reported the ACA reaction of linear α,β-unsaturated esters, catalyzed by the Rh/(*S*)-BINAP **L1** catalyst, with high *ee* values (89–96% *ee*), using conditions similar to those described for enones. The asymmetric induction seems to be dependent on the steric hindrance of the ester moiety. However, for some linear esters, the more reactive arylborates, generated *in situ* by lithiation of aryl bromides followed by treatment with trimethoxyborane, are unavoidable reagents to achieve higher yields (Scheme 113).[311] Recently, Darses and coworkers[313] described the use of potassium organotrifluoroborates as alternative boron reagents, leading to the β-substituted esters with high yields and *ee* values (Scheme 113). An alternative methodology was developed by Inoue,[314] using aryltrialkoxysilanes as cheap, less toxic, and easy-to-handle donors in the presence of a chiral rhodium complex generated from $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP **L1** (Scheme 113).



Scheme 113 General methods for the ACA reaction on linear α,β-unsaturated esters.

β-Substituted unsaturated esters, with aryl or heteroaryl groups, were also evaluated in the ACA reaction, using various rhodium complexes (Scheme 114). Miyaura and coworkers[315] described the 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated esters **14**, mediated by a cationic rhodium(I)-chiraphos **L54** system, yielding β-diaryl carbonyl compounds **15** with great enantioselectivities (up to 94% *ee*). This quite versatile methodology, tolerant toward various functional groups, was applied to the preparation of key intermediates (**16**) in the synthesis of selective endothelin antagonists. Similarly, Carreira and coworkers[316] developed Rh complexes, modified by chiral diene **L55**, which were active in the preparation of 3,3-diaryl propanoates, as well as 3-aryl-3-heteroarylpropanoates with moderate-to-high yields and high enantioselectivities by the ACA reactions of various ester acceptors with a wide range of boron donors. Hayashi and coworkers[317] reported the asymmetric 1,4-addition of arylboronic acids to (*E*)-methyl 2-cyano-3-aryl propenoates **17** in the presence of a Rh catalyst coordinated with (*R,R*)-Ph-bod* diene **L18a**. This approach was used for the synthesis of (*R*)-tolterodine.

Asymmetric 1,4-addition was also applied to various β-functionalized-α,β-unsaturated esters (Scheme 115). Thus, fumaric acid diesters **18** were used as substrates in this transformation with high *ee* values, using a rhodium complex modified by the chiral norbornadiene **L56**, bearing mesitylmethyl groups.[318] β-phtaliminoacrylate esters **20** were also investigated as acceptors, using a hydroxorhodium catalyst coordinated to (*S,S*)-Bn-tfb diene ligand **L57**,[319] thus yielding β-aryl-β-*N*-phthaloylamino acid esters **21**, which could readily be converted into the β-amino-acid derivatives **22** with no loss of enantiomeric purity. A similar Rh complex, coordinated with (*S,S*)-Fc-tfb diene ligand **L58**, was applied in the high-yielding addition of arylboroxines onto various β-alkoxyacrylate esters **23**, thus affording β-alkoxy-β-arylcarboxylic acid esters **24** as interesting structural components in natural products and pharmaceuticals with outstanding *ee* values.[320] Recently, Hayashi and Shintani[321] reported the formation of quaternary carbon stereocenters at the β-position of esters through a 1,4-addition of sodium tetraarylborates to β,β-disubstituted



Scheme 114 Rh-mediated ACA reaction of β-aryl-α,β-unsaturated esters.

α,β-unsaturated esters **25** by tuning the ester group and using a readily available chiral diene ligand **L59**. This reaction was applied to the construction of 3,3-disubstituted-1-indanones **28** by performing the arylation reaction under aprotic conditions.

Many examples of Rh-mediated ACA on esters or lactones were reported in the literature toward the synthesis of pharmaceutically active compounds, such as (*R*)-Baclofen,[322] (*R*)-Rolipram,[323] or (*R*)-tolterodine, which was synthesized from a 2-cyano-3-arylpropenoate **29** (Scheme 116).[315]

Interestingly, the Rh-catalyzed ACA reaction was also developed on a kilogram scale as part of a drug development program,[324] proposing a number of scale-up issues such as the use of a minimum amount of isopropanol to avoid protodeboronation and of an oxidant to facilitate rhodium removal (Scheme 117).

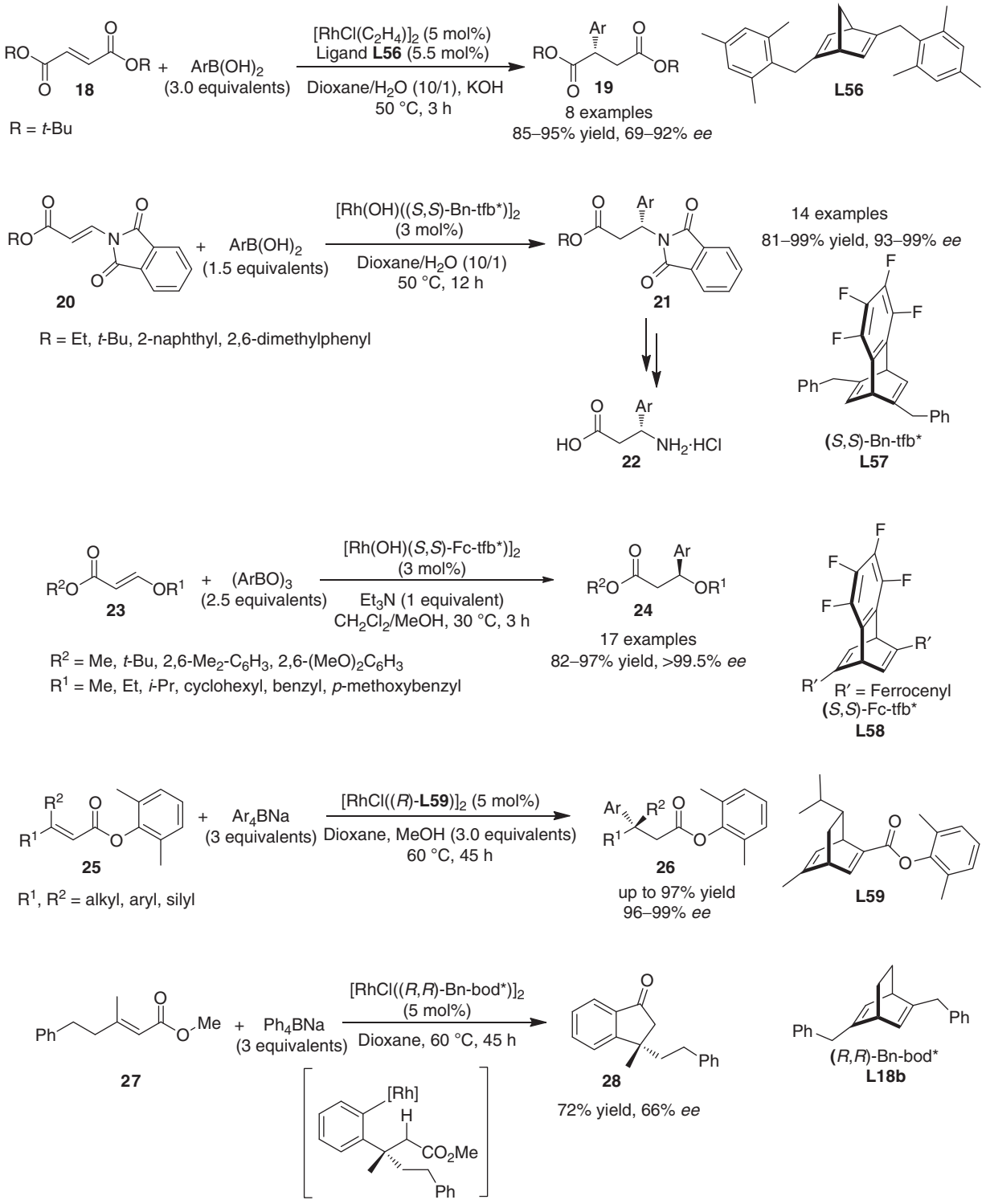
Alkylidene Meldrum's acid derivatives **30** proved also to be excellent acceptors for conjugate addition, affording a wide range of products that could be further transformed. Thus, Fillion and coworkers[325] developed a series of ambiphilic reagents based on 3-(tributylstannyl)-2-propenyl acetates and carbonates **31**, in which the vinyl-tin bond acts as a base and the allyl acetate as a Pd-activated electrophile. Thus, the 1,4-addition of functionalized vinyltin reagents to alkylidene Meldrum's acids, followed by a Pd-mediated intramolecular allylation, provides a promising route toward vinyl-substituted γ-lactones **33** through O-alkylation and vinylcyclo propanes **34** via C-alkylation (Scheme 118).[326]

4.04.3.1.2.2 α,β-Unsaturated lactones

Compared to linear esters, the asymmetric conjugation addition to cyclic α,β-unsaturated esters is well performed with arylboronic acids in the presence of the Rh/(*S*)-BINAP system,[309,310] with high asymmetric induction (Scheme 119). Six-membered cyclic ester **35** (5,6-dihydro-2*H*-pyran-2-one) reacts with arylboronic acids to afford the corresponding arylation products in high yields with 97–98% *ee*, although five membered-lactones usually give poorer yields.

The ACA reaction of arylboronic acids on 5,6-dihydro-2*H*-pyran-2-one **35** was also performed with Rh catalysts coordinated to various ligands, already described for the reaction on cyclic enones. The most pertinent results are summarized in Scheme 120. Diphosphine ligands such as the electron-deficient atropoisomeric SYNPHOS analogs **L12**,[266] optically active diene ligands (**L24**),[272h] chiral chain diene ligand **L26**[273a] or **L27**,[273b] phosphine-olefin ligand **L28**,[275a,c] or sulfur-based ligands such as bis-sulfoxide ones **L38** and **L39**,[280a] as well as sulphur-olefin derivatives[283b,284] (**L44**, **L55**) proved to be highly enantioselective with moderate to high yields.

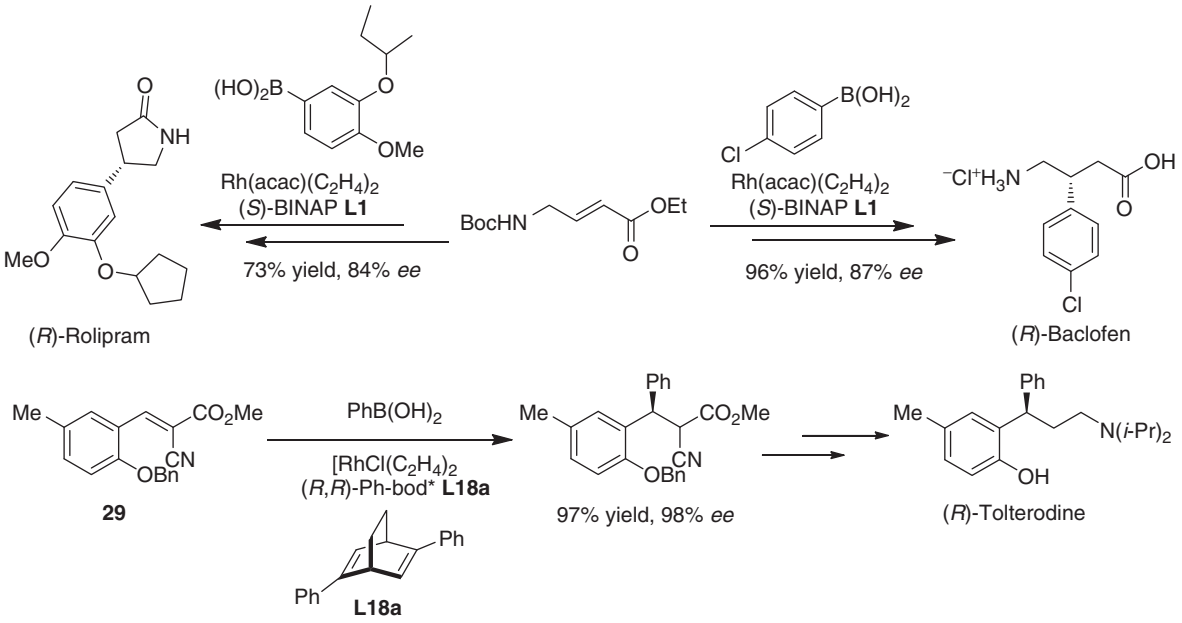
Coumarin derivatives **36** are also good acceptors in the Rh-promoted conjugate addition. However, high excess of boronic acids (up to 10 equivalents) were required with these less reactive substrates to achieve high conversions. Outstanding *ee* values, superior to 99.1%, were achieved using (*R*)-Segphos **L61** as chiral ligand (Scheme 121).[327] This reaction on coumarin acceptors



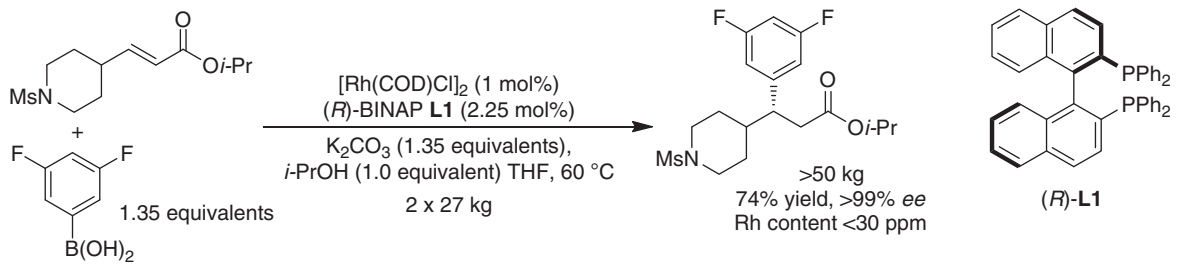
Scheme 115 Rh-mediated ACA reaction of β-functionalized-α,β-unsaturated esters.

was successfully applied to the synthesis of (*R*)-tolterodine with an excellent asymmetric induction (up to 99.6%).[325] Recently, Carreira and coworkers[272c] proposed the use of the chiral carvone-derived [2.2.2] diene ligand **L19** with 98% *ee* (Scheme 121).

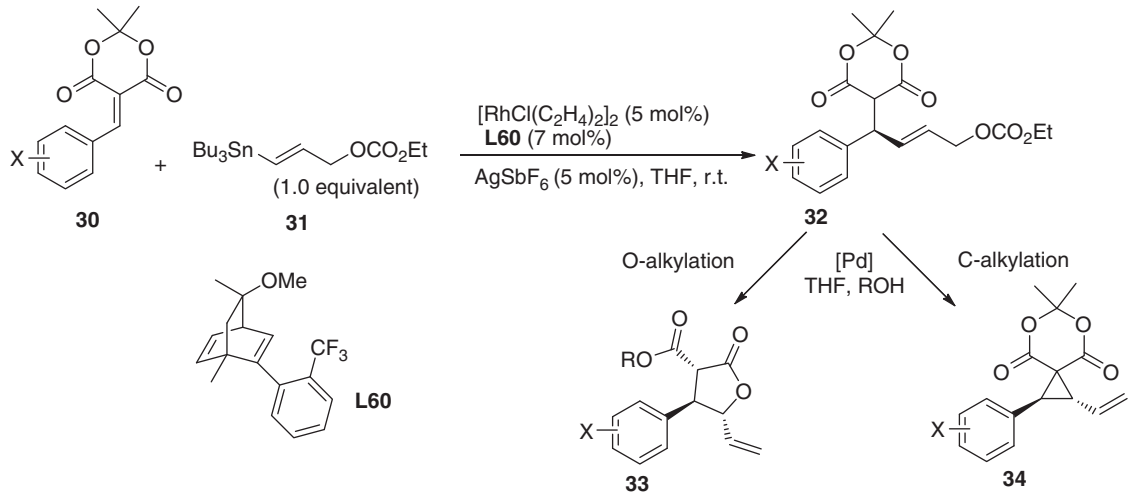
Various organozinc derivatives were also used as nucleophiles for the 1,4-addition on cyclic α,β-unsaturated esters. Enantiomerically pure rhodium complex **L52**, to which the chiral diene 1,5-diphenyl-1,5-cyclooctadiene coordinates with one of the enantiotopic faces, catalyzed the addition of phenylzinc chloride to 5,6-dihydro-2*H*-pyran-2-one **35** with *ee* up to 98%



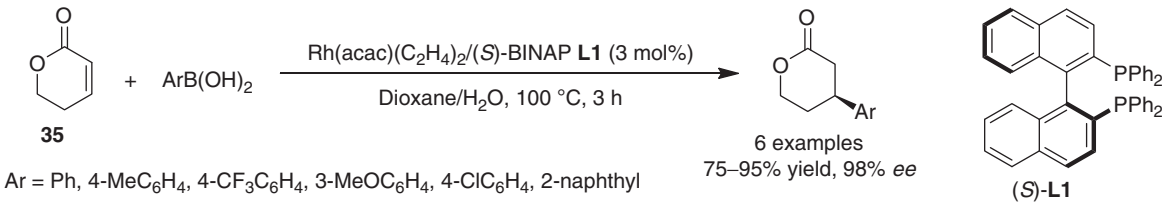
Scheme 116 Application of the ACA reaction on esters toward the synthesis of biologically active molecules.



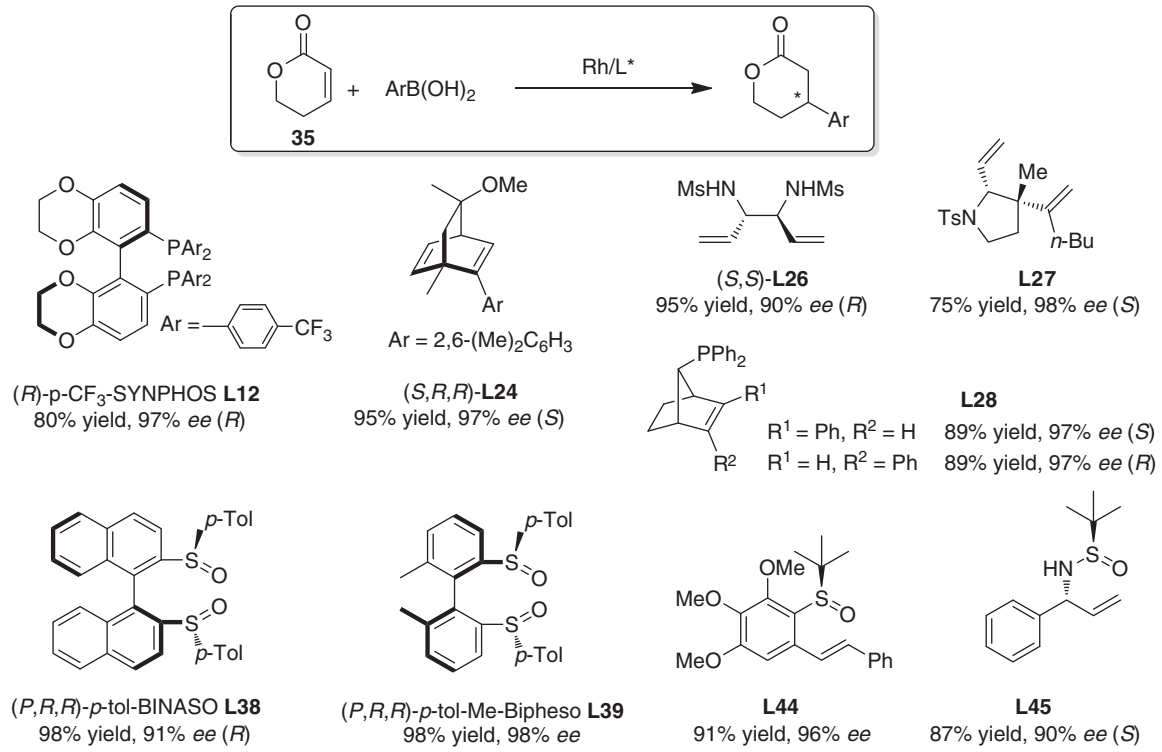
Scheme 117 Enantioselective conjugate addition on a kilogram scale.



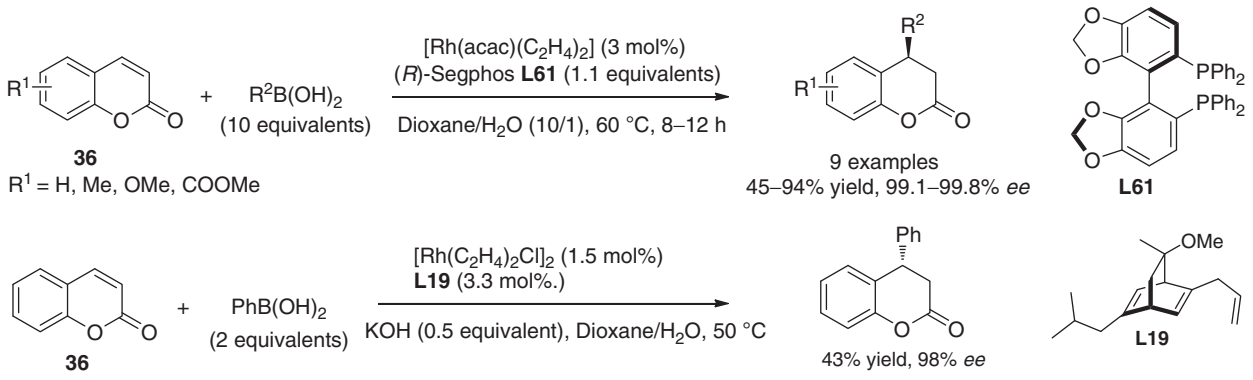
Scheme 118 Synthesis of γ-lactones and vinylcyclopropanes through a tandem addition/allylation process.



Scheme 119 ACA reaction of organoboron reagents on α,β-unsaturated lactones.



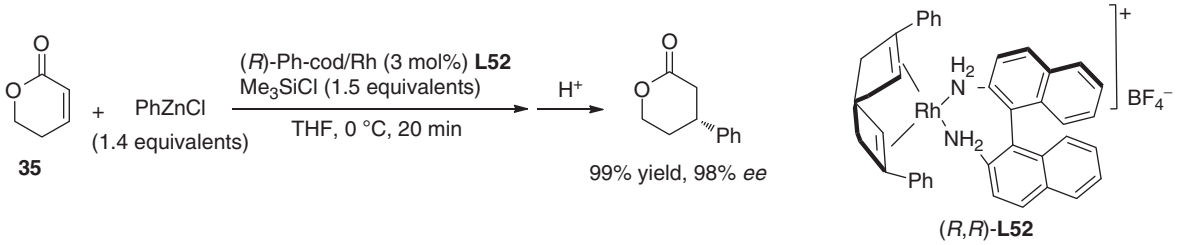
Scheme 120 Pertinent enantiopure ligands in the ACA reaction to 5,6-dihydro-2H-pyran-2-one.



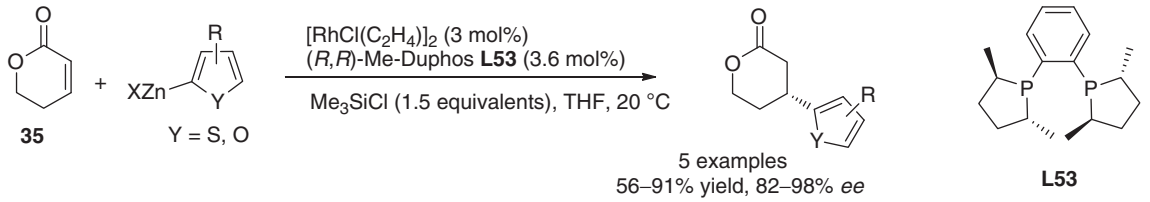
Scheme 121 ACA reaction of organoboron reagents on coumarin derivatives.

(Scheme 122).[306] The high asymmetric induction demonstrates that the Ph-cod ligand generates an efficient chiral environment around rhodium during the catalytic reaction.

A range of 2-heteroaryzinc donors, combined with chlorotrimethylsilane, also underwent highly enantioselective conjugate addition, with a complex-derived [RhCl(C_2H_4)$_2$]/Me-Duphos **L52**,[307] which proved to be superior to established catalysts for this challenging reaction (Scheme 123).



Scheme 122 ACA reaction of organoboron reagents on α,β-unsaturated lactones.

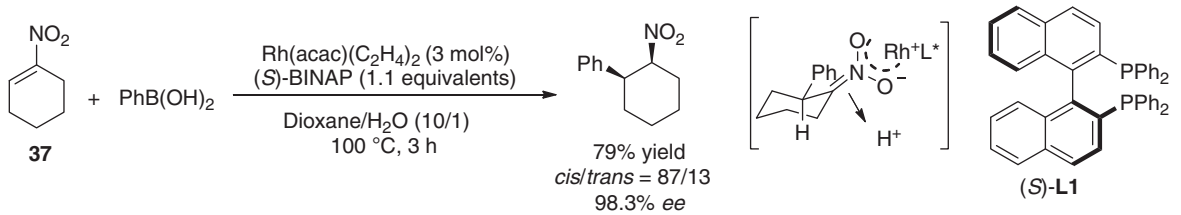


Scheme 123 Rh-mediated ACA reaction of heteroaromatic organozinc reagents to esters.

4.04.3.1.3 Nitroolefins

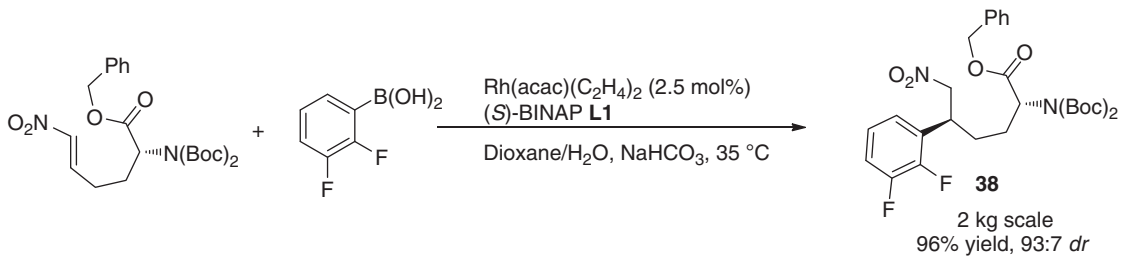
Owing to the great potential of nitro compounds in organic synthesis,[328] the ACA of organometallic reagents to nitroalkenes proved to be an attractive approach. Compared to the successful copper-catalyzed additions of dialkylzinc to nitroolefins, only few examples have been reported with rhodium catalysts, likely because of the challenge in controlling the reaction stereoselectivity.

In 2000, Hayashi et al.[329] reported the 1,4-addition of phenylboronic acid to 1-nitrocyclohexene **37**, in the presence of a Rh complex of (*S*)-BINAP **L1**, through the formation of a rhodium nitronate intermediate with good yield and high stereoselectivity (Scheme 124). Treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol leads to the thermodynamically more stable *trans* isomer (*trans*/*cis* = 97/3) with the same enantiomeric purity.



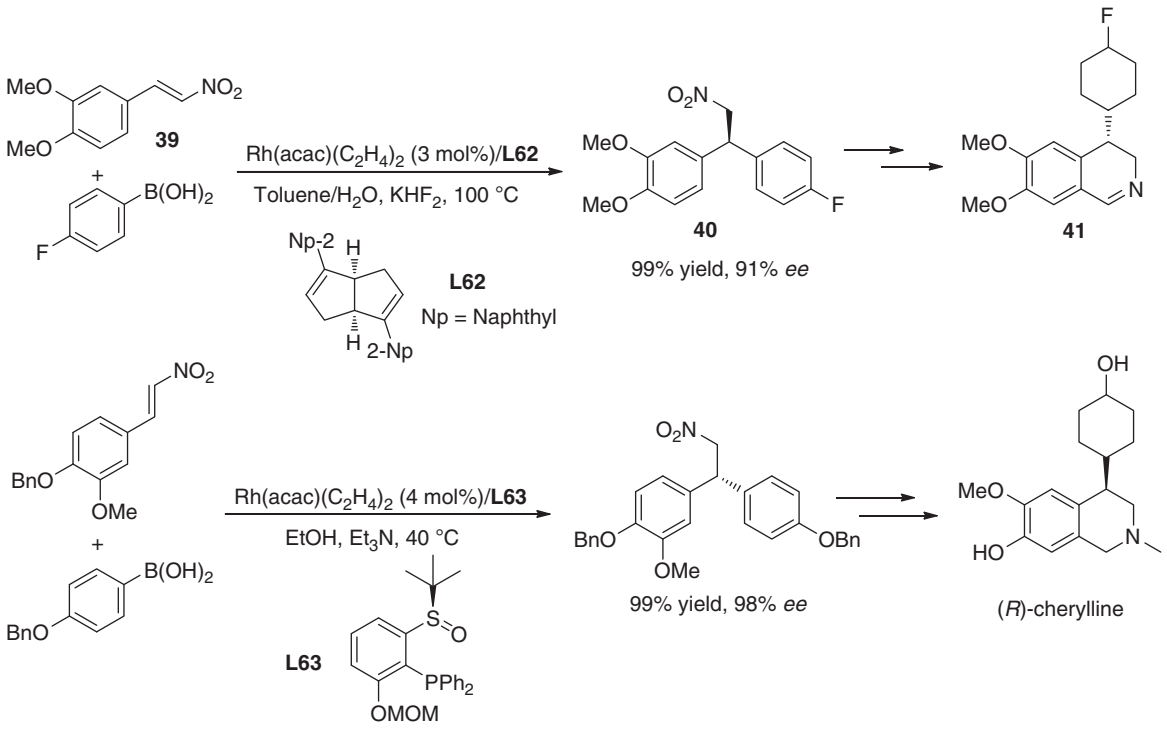
Scheme 124 1,4-Addition of phenylboronic acid to 1-nitrocyclohexene.

This transformation could be extended to linear nitroalkenes and was successfully applied by the Merck research group for the synthesis of a key intermediate **38** in the synthesis of Telcagepant used in a migraine headache treatment (Scheme 125).[330]



Scheme 125 1,4-Addition of boron reagent to linear nitroolefins.

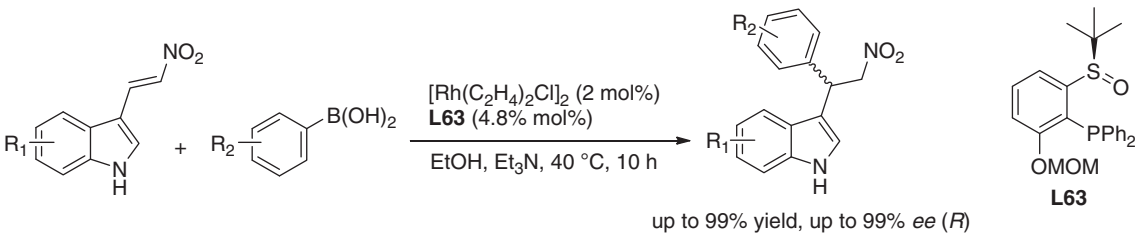
The challenging 2-nitrostyrenes were also investigated as acceptors (Scheme 126). Lin and coworkers[331] described efficient Rh-catalyzed ACA reactions on 2-nitrostyrene analogs (up to 97% *ee*), using a C_2-symmetric chiral diene as ligand **L62** and



Scheme 126 Rh-promoted 1,4-addition of arylboronic acids to nitroarylstyrenes.

potassium trifluoroborates as organoboron reagents (generated *in situ* from boronic acids and potassium acid fluoride). Their conditions were used for the successful transformation of nitroalkene **39** into pharmaceutically interesting isoquinoline derivative **41**. This 1,4-conjugate addition on such acceptors could also be performed, using *tert*-butanylphosphine ligand **L63**,[332] with excellent yields (up to 99%) and enantioselectivities (up to 98%) under quite mild conditions. This reaction was further used for the synthesis of (*R*)-cherylline.

The scope of the Rh-mediated ACA reaction was extended to 2-nitroalkylstyrenes[329,333] and to 2-nitroheteroarylstyrenes.[331,334] For instance, Liao and coworkers[334] reported an efficient approach to optically pure α-aryl-3-indolylnitroethanes through the ACA reaction of boron compounds to indolylnitroalkenes, thanks to the use of ligand **L63** (Scheme 127).

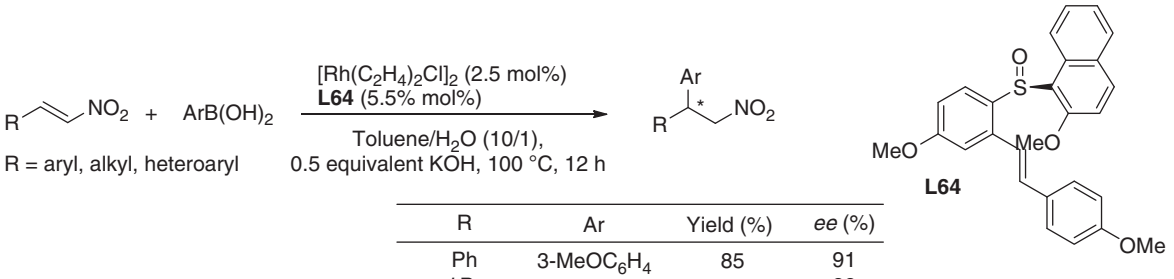


Scheme 127 Synthesis of enantioenriched α-aryl-3-indolylnitroethanes through ACA reaction.

Recently, Wang et al.[331] developed an efficient ACA process, which tolerates a broad scope of aryl, alkyl, and heteroaryl nitroalkenes in the presence of olefin-sulfoxide ligand **L64** with quite good enantioselectivities (Scheme 128).

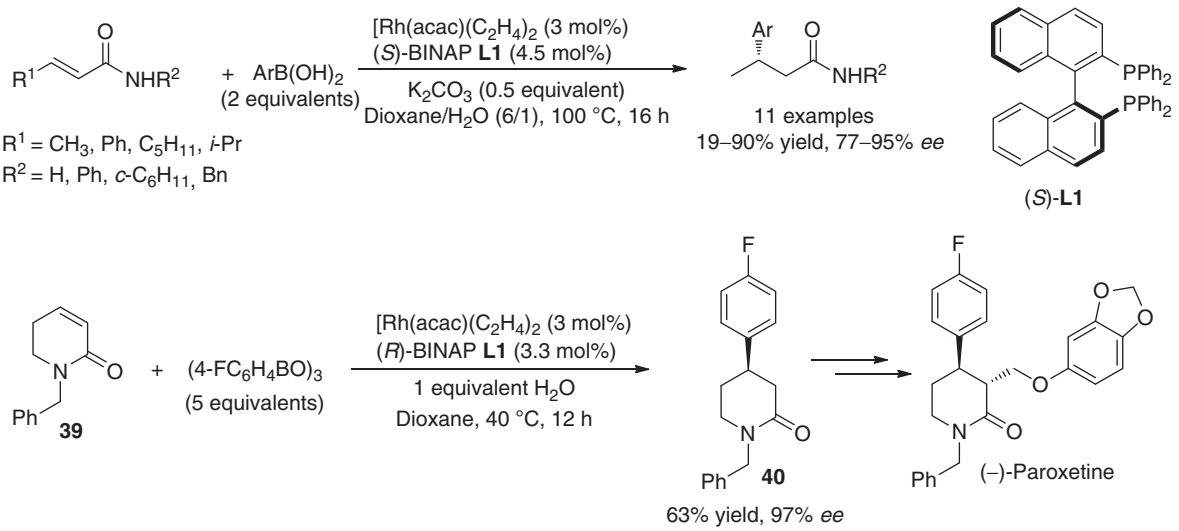
4.04.3.1.4 Amide/Lactame

Linear and cyclic α,β-unsaturated amides were also used as acceptors in Rh-mediated ACA reaction under standard conditions, although being less reactive than enones or enoates. Initially, the 1,4-addition of α,β-unsaturated amides was explored by Miyaura[335] under standard conditions, yielding β-arylamides with pertinent asymmetric induction with Rh/(*S*)-BINAP **L1** catalyst (Scheme 129). The addition of K_2CO_3 was essential to improve the conversions. In parallel, Hayashi[336] performed the reaction on protected lactames, changing boronic acids to organoboroxines, thus yielding optically active 4-aryl-2-piperidinones. Noteworthy, this approach was applied for the obtention of a key synthon **40** in the synthesis of the antidepressant and anti-Parkinson's disease drug paroxetine through a 1,4-addition on 5,6-dihydro-2-(1H)-pyridinone **39** (Scheme 129).



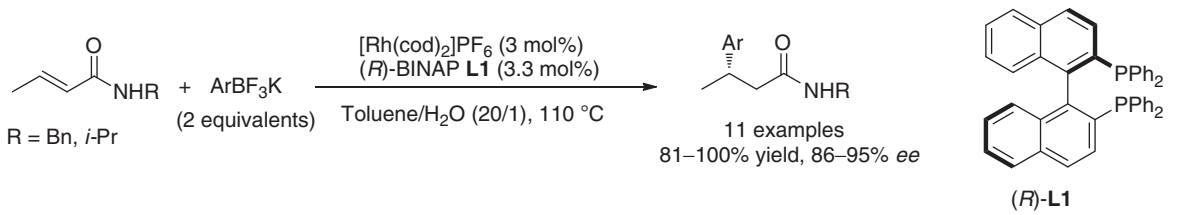
R	Ar	Yield (%)	*ee* (%)
Ph	3-$MeOC_6H_4$	85	91
i-Pr	4-MeC_6H_4	85	88
c-C_6H_{11}	4-MeC_6H_4	71	90
2-Thienyl	3-$MeOC_6H_4$	84	87

Scheme 128 Efficient and versatile ACA process.



Scheme 129 Rh-promoted ACA reaction on α,β-unsaturated amides and lactames.

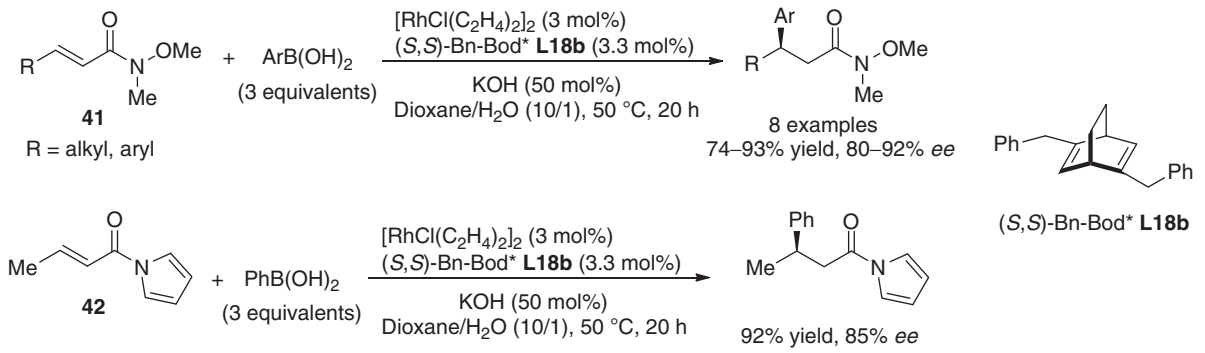
Alternatively, highly stable organotrifluoro(organo)borates proved to be very efficient partners in the 1,4-additions to enamides, being more reactive than their boronic acid counterparts, achieving high yields and good to excellent enantiomeric excesses with no base (Scheme 130).[337]



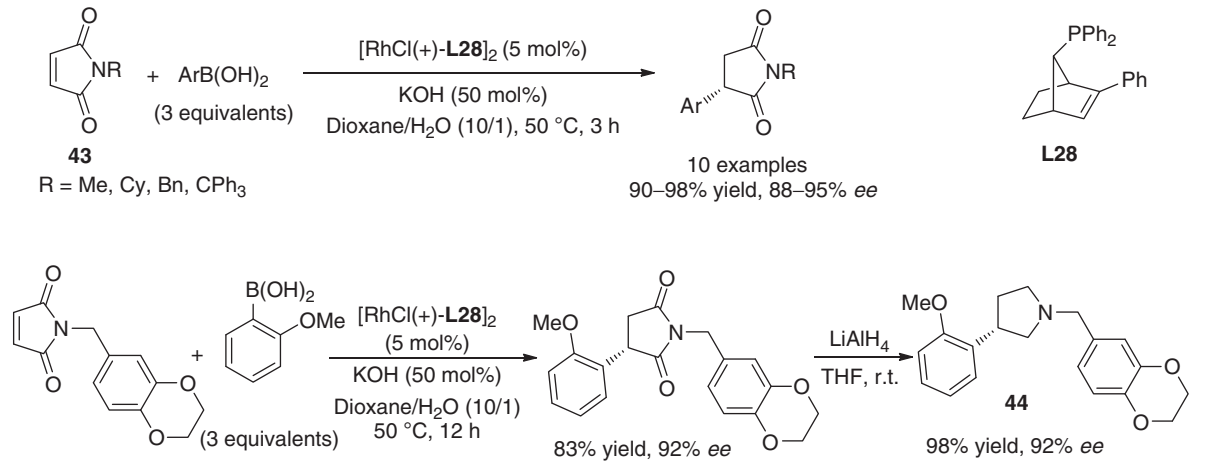
Scheme 130 Organotrifluoro(organo)borates as relevant alternatives in the ACA reaction to enamides.

Weinreb amides[338] (*N*-methoxy-*N*-methylamides **41**), which are excellent acylating agents, could also be efficiently transformed into useful optically enriched β-substituted amides through a 1,4-addition reaction via a Rh/diene complex (Scheme 42-AN). This process was extended to the acylpyrrole **42**, with high yield and 85% *ee* (Scheme 131).

Maleimides were also reported as potential acceptors. Hayashi and coworkers[275a] described the use of a chiral phosphorus-olefin hybrid ligand **L28** as relevant in the Rh-mediated 1,4-addition of organoboron reagents to maleimides **43** with excellent yields and enantioselectivities. This reaction was successfully applied to the enantioselective synthesis of biologically active compounds, such as the enantiomer of a potent α-2-adrenoreceptor antagonist **44** (Scheme 132).

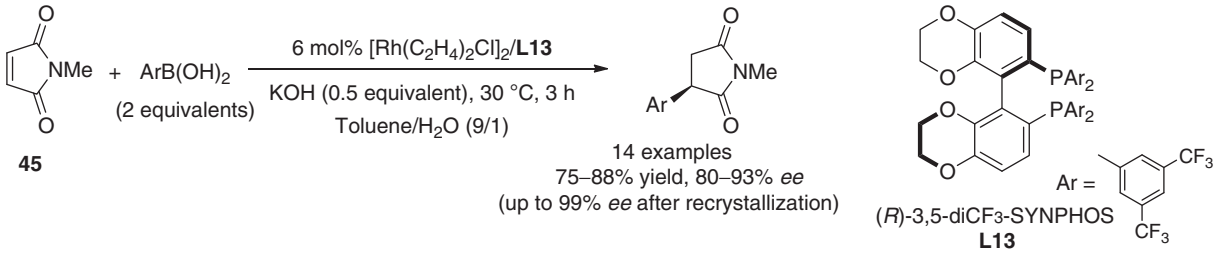


Scheme 131 Rh-promoted ACA reaction on Weinreb amides and acylpyrrole.



Scheme 132 Rh-promoted ACA reaction on maleimides.

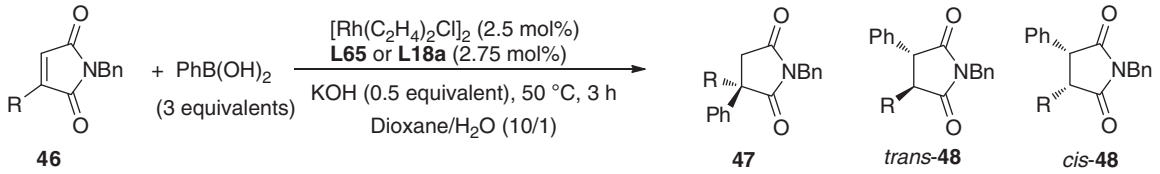
Recently, the challenging *N*-methylmaleimides **45** were used as acceptors in 1,4-addition of arylboronic acids under mild conditions, using the (*R*)-3,5-diCF$_3$-SYNPHOS ligand **L13**,[15] thus affording various enantioenriched 3-substituted succinimide synthons of biological interest, which could be upgraded up to 99% after a single crystallization (Scheme 133).

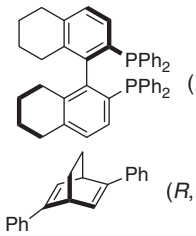


Scheme 133 Asymmetric 1,4-addition of organoboron reagents to *N*-methylmaleimides.

Hayashi and coworkers[286] also reported the challenging enantioselective construction of quaternary carbon stereocenters through the 1,4-addition of arylboronic acids to 3-substituted maleimides **46**, thus yielding 3,3-disubstituted succinimides in high regio- and enantioselectivities (Scheme 134). Interestingly, the regioselectivity could be controlled by the judicious choice of the ligand. Although (*R*)-H8-BINAP **L65** led to the preferential formation of the 3,3′-substituted product **47**, the 2,3 bis-substituted product **48** was obtained with the chiral diene (*R*)-Ph-bod* **L18a**, owing to the steric hindrance between an aryl group on the Rh and the R substituent on maleimide.

Interestingly, oxobutenamides proved to be challenging substrates for conjugate addition, particularly concerning regioselectivity issues. The highly regio- and enantioselective addition of organoboron reagents to these substrates requires a catalyst able to distinguish not only enantiotopic π-faces but also the subtle electronic differences of each conjugate acceptor. The key parameter to

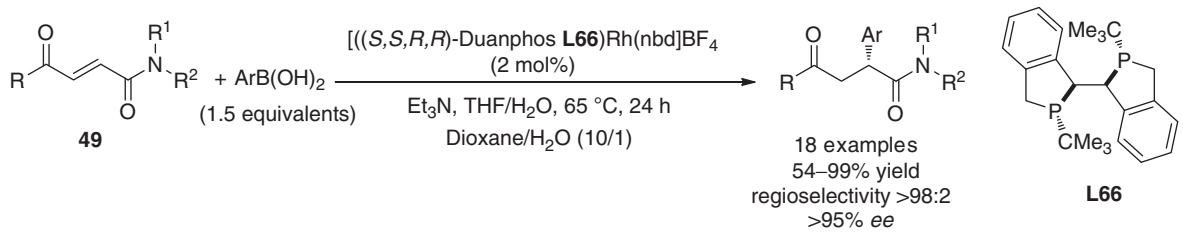




	yield (%)	47/48 *(trans/cis)*	*ee* 47 *(%)*	*ee* 48 *(%) (trans,cis)*
R = Me	98	**87**/13 (2.3/1)	**97**	–19, 96
R = Et	98	**81**/19 (2.8/1)	**96**	–10, 94
R = Me	94	15/**85** (1/2.3)	97	**83, >99**
R = Et	94	11/**89** (1/1.4)	93	**79, 99**

Scheme 134 Ligand effect for the regiocontrol of the ACA on 3-substituted maleimides.

great selectivity relies on the use of sterically demanding P-chiral phosphines, such as Duanphos **L66**. Under optimized conditions, a variety of *N,N*-disubstituted 4-oxobutenamides **49** proved to be effective coupling partners with various arylboronic acids to afford 2-aryl-4-oxobutanamides in high regioselectivity (>98/2) and enantiomeric purity (>95% *ee*) (Scheme 135). The optically active obtained products are synthetically versatile intermediates, which could be functionalized on either the carbonyl or amide with minimal erosion of enantiomeric purity.



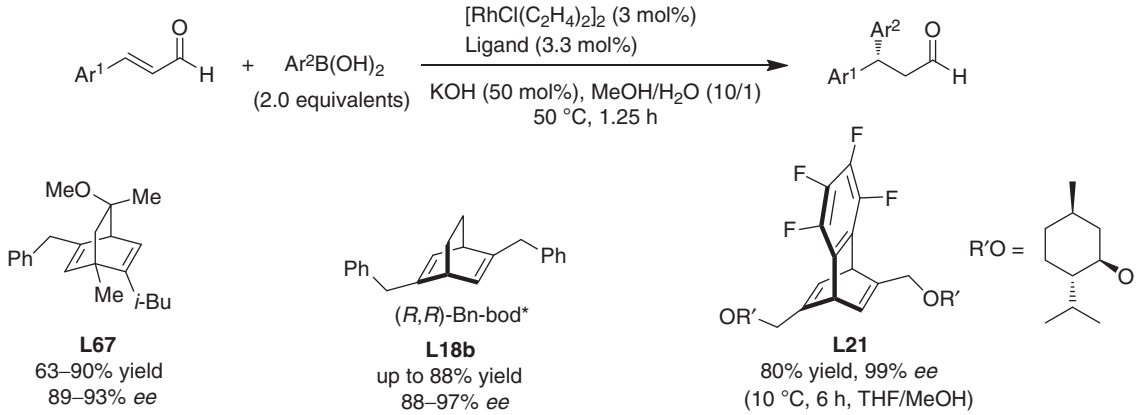
Scheme 135 Regioselective ACA to oxobutenamides.

4.04.3.1.5 Miscellaneous Michael acceptors

4.04.3.1.5.1 α,β-Unsaturated aldehydes

Aldehydes are among the most versatile functional groups in organic synthesis. However, enal compounds constitute a challenging class of substrates for Rh-mediated ACA owing to the high reactivity of aldehydes (1,4-addition vs. 1,2-addition).

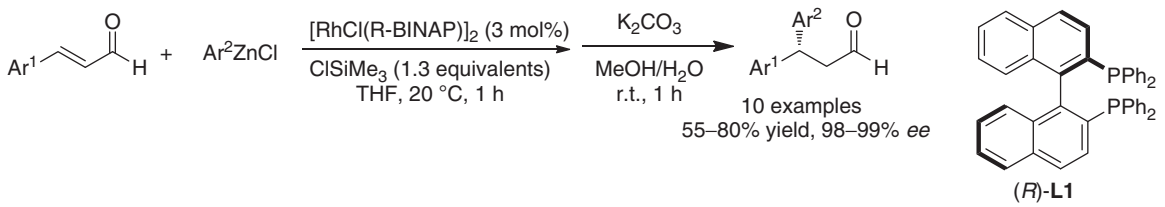
Pertinent Rh catalysts coordinated to various chiral dienes (**L67** or **L18b**)[339,340] were reported for the selective 1,4-addition of arylboronic acids to *β*-aryl-*α,β*-unsaturated aldehydes, thus yielding enantiomerically highly enriched *β,β*-diaryl propanals (Scheme 136). This methodology is particularly attractive, generating stereogenic centers with two aryl substituents (found in



Scheme 136 Rh-mediated ACA of arylboronic acids to enals.

many pharmaceuticals and natural products) and releasing aldehydes, which could further be modified. Noteworthy, a hydroxorhodium catalyst coordinated to chiral tetrafluorobenzobarrelene ligand **L21** proved also to be a highly efficient ligand for the 1,4-addition of boron reagents to an enal.

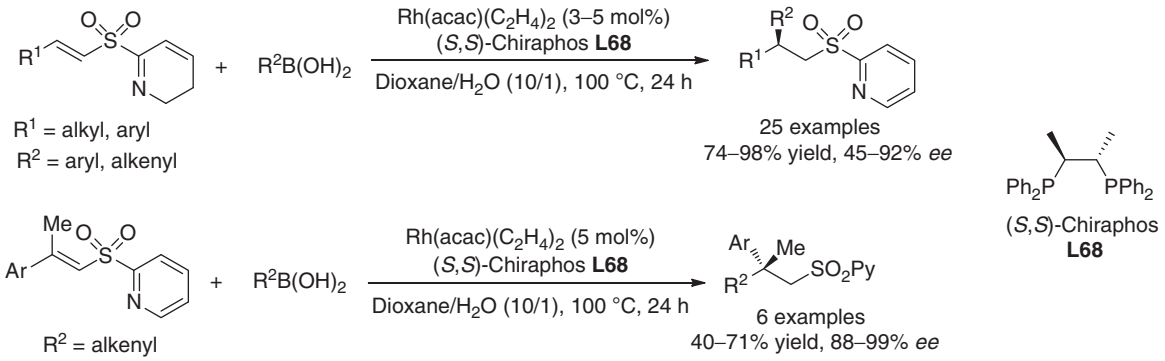
Parallel to this method, Hayashi and Tokunaga[341] described the asymmetric 1,4-addition of arylzinc chlorides to (*E*)-3-arylpropenals with high *ee* values (up to 99%), using a rhodium-(*R*)-BINAP **L1** catalyst and chlorotrimethylsilane, which is essential to achieve high yields in *β*,*β*-diaryl propanals (Scheme 137).



Scheme 137 Rh-catalyzed ACA of arylzinc chlorides to 3-arylpropanals.

4.04.3.1.5.2 *α,β-Unsaturated sulfones*

Owing to the great versatility of sulfones in organic synthesis, the ECA reactions to *α*,*β*-unsaturated sulfones were investigated. Despite the unsuccessful attempts of Hayashi,[342] the key for this challenging reaction relies on the use of an appropriately rhodium-coordinating *α*,*β*-unsaturated heteroaromatic sulfones as the key controlling moiety and (*S*,*S*)-Chiraphos **L68** as the optimal chiral ligand (Scheme 138).[343] These pyridylsulfones provide a general, high yielding, and stereoselective route (76–92% *ee*) for producing *β*-substituted sulfones, which are appealing building blocks for Julia–Kociensky olefination or alkylation/desulfonylation sequences. This methodology was applied to the addition of alkenylboronic acids to *β*,*β*-disubstituted *α*,*β*-unsaturated 2-pyridylsulfones, thus generating quaternary stereocenters with up to 99% *ee*.[344]



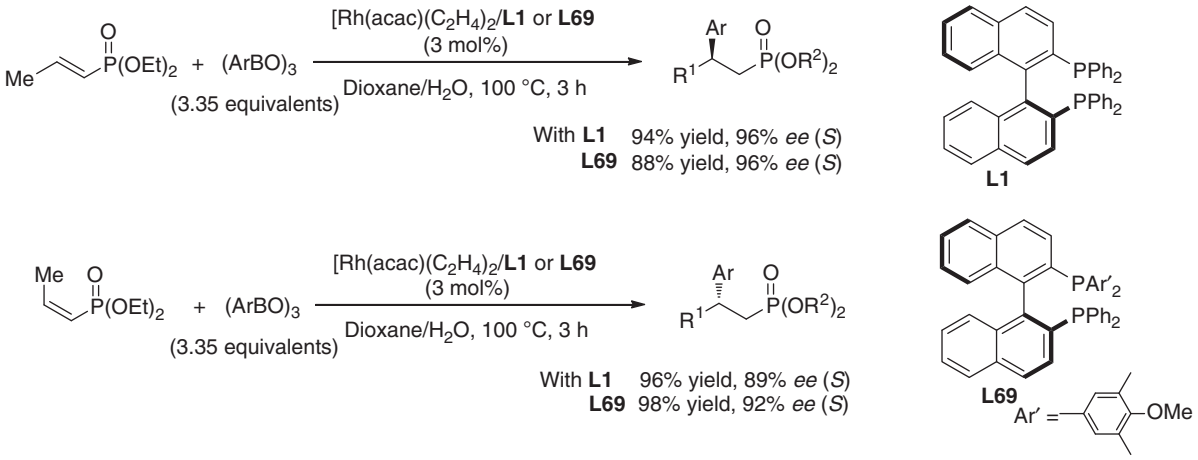
Scheme 138 Enantioselective conjugate addition reactions to *α*,*β*-unsaturated sulfones.

4.04.3.1.5.3 *Alkenylphosphonates*

Optically active phosphonic derivatives are promising compounds owing to their synthetic interest as chiral building blocks as well as their potential biological activity. A synthetic route toward these useful intermediates is based on the Rh-catalyzed asymmetric 1,4-addition to *α*,*β*-unsaturated phosphonates by use of triarylcyclotriboroxanes as arylating reagents instead of arylboronic acids (Scheme 139).[345] Promising asymmetric inductions were achieved with the Rh/(*S*)-BINAP **L1** complex, and could be slightly increased when the reaction is catalyzed by a rhodium complex coordinated with unsymmetrially substituted BINAP ligand, (*S*)-*μ*-BINAP **L69**. Moreover, the influence of the alkene's geometry (*E* vs. *Z*) was also studied, showing that using the same optically enantiopure ligand, the *Z*-and *E*-isomers gave rise to opposite enantiomers.

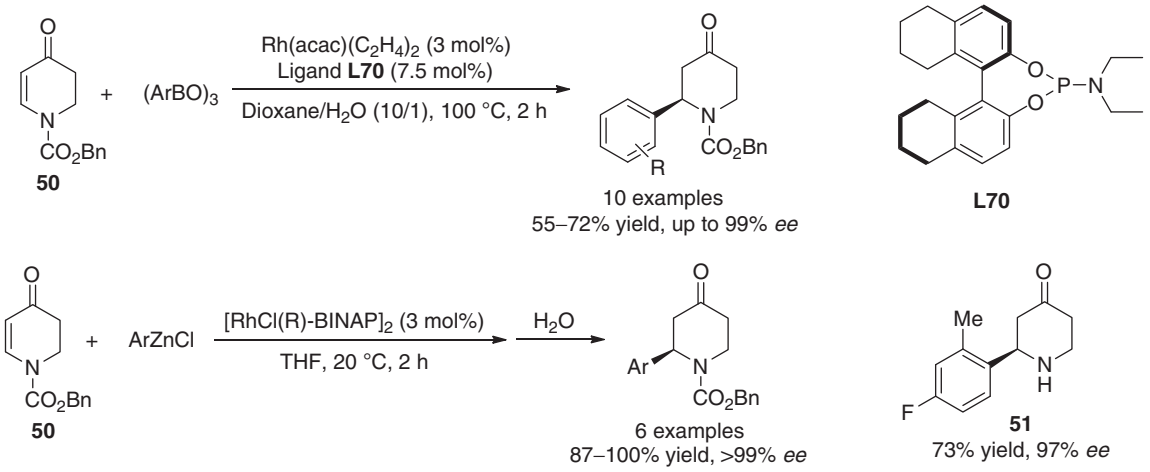
4.04.3.1.5.4 *α,β-Unsaturated piperidones*

Asymmetric 1,4-addition of organometallic reagents to 2,3-dihydro-4-pyridones was also investigated as a promising route to synthetically and biologically interesting 2-arylpiperidines via various strategies (Scheme 140). The conjugate addition of arylboroxines to the pyridone **50** was developed with an Rh/phosphoramidite **L70** catalyst.[346] Various sterically and electronically diverse arylboroxines were used, yielding the chiral 2-aryl-4-piperidones with high isolated yields (82–92%) and excellent *ee* values (up to 99%). Hayashi and coworkers[347] reported the addition of various organozinc nucleophiles to piperidone **50**,



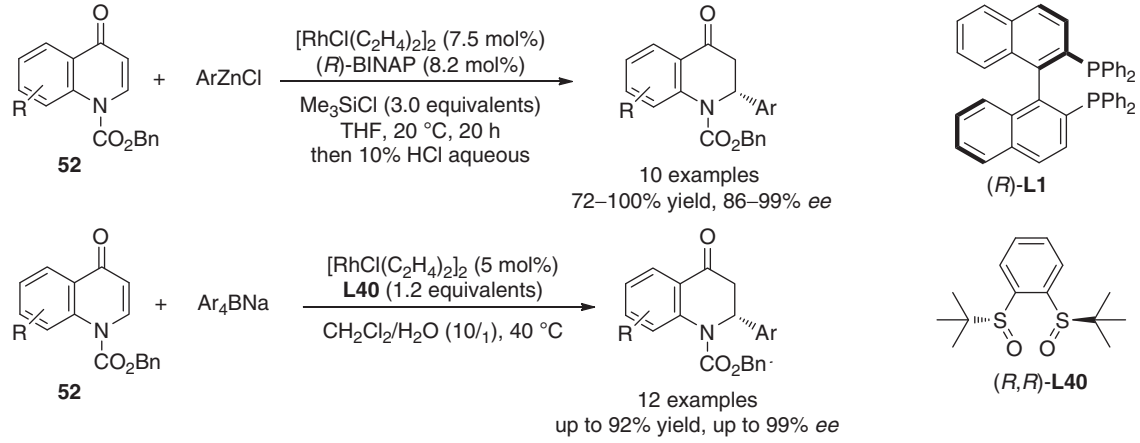
Scheme 139 Rh-mediated ACA reaction of organoboron reagents onto alkenylphosphonates.

catalyzed by a rhodium/(*R*)–BINAP **L1** complex under very mild conditions with *ee* values superior to 99%. This methodology was further used for the asymmetric synthesis of tachykinin antagonists **51**.



Scheme 140 Asymmetric 1,4-addition of organometallic reagents to 2,3-dihydro-4-pyridones.

Recently, the scope of this methodology was extended to 4-quinolones **52** (Scheme 141). Thus, the 2-aryl-2,3-dihydro-4-quinolones could be obtained with high *ee* (86–99%), using (*R*)-BINAP **L1** as ligand and arylzinc reagents, and yields were

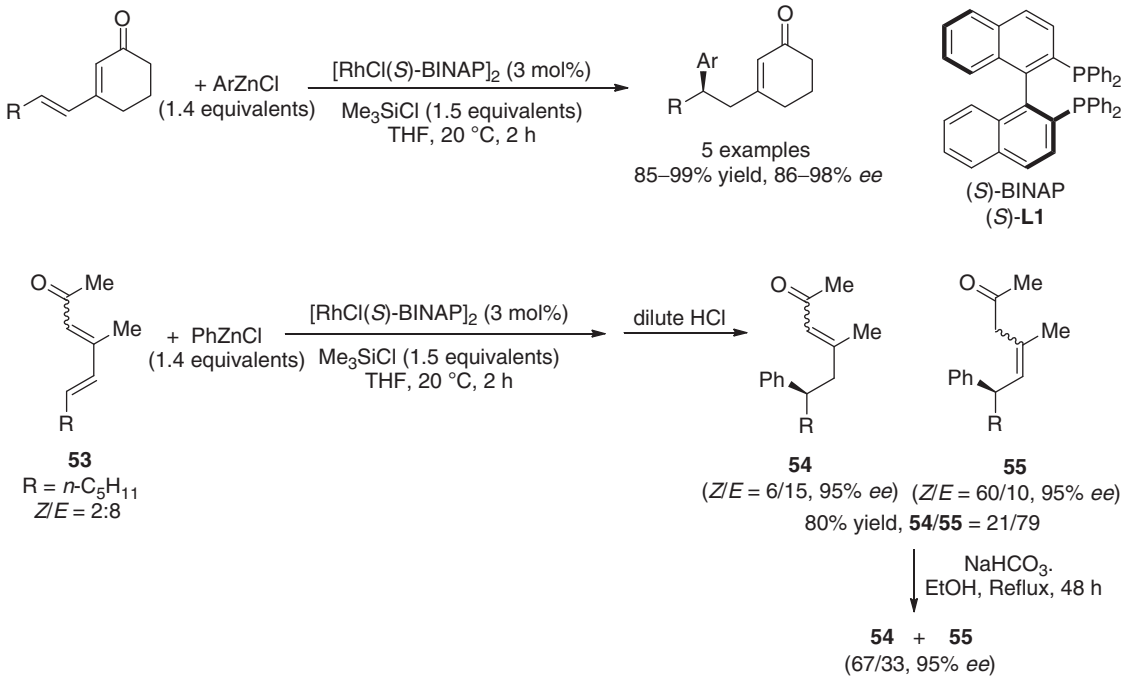


Scheme 141 Asymmetric 1,4-addition of organometallic reagents to quinolones.

improved with chlorotrimethylsilane.[348] The reaction could also be performed with (*R*,*R*)-1,2-bis(*tert*-butylsulfinyl)benzene **L40** as a simple ligand using sodium tetraarylborates as nucleophiles, under mild conditions, affording the 1,4-adducts with moderate-to-high yields and high-to-excellent enantioselectivities.

4.04.3.1.6 Extended Michael acceptors

Although 1,4-conjugate additions constitute a well-understood process, the 1,6-additions onto $\alpha,\beta,\gamma,\delta$-di-unsaturated carbonyls are particularly challenging because of the difficulty in controlling the regioselectivity because of the various competitive routes as well as the asymmetric induction. In 2005, Hayashi and coworkers[349] reported the first example of a regioselective asymmetric 1,6-addition to 2,4-dien-1-ones, thus generating a stereogenic center at the C5 center. Although arylboronic acids or anionic aryltitanium reagents gave poor results, the use of the reactive arylzinc reagent PhZnCl in conjunction with chlorotrimethylsilane in the presence of the Rh/BINAP **L1** catalyst allows the 1,6-addition to various 2,4-dien-1-ones with up to 98% *ee* (Scheme 142). The β-disubstitution proved to be crucial to avoid the formation of the 1,4-addition product. The addition on the linear dienone **53** (4-methylundeca-3,5-dien-2-one) was also achieved with perfect 1,6-selectivity, affording after acidic hydrolysis a mixture of olefinic isomers in a 21/79 ratio, high yield, and 95% *ee* for each compound. This ratio could be shifted to 67/33 by treatment with sodium bicarbonate, without any erosion of optical purity.

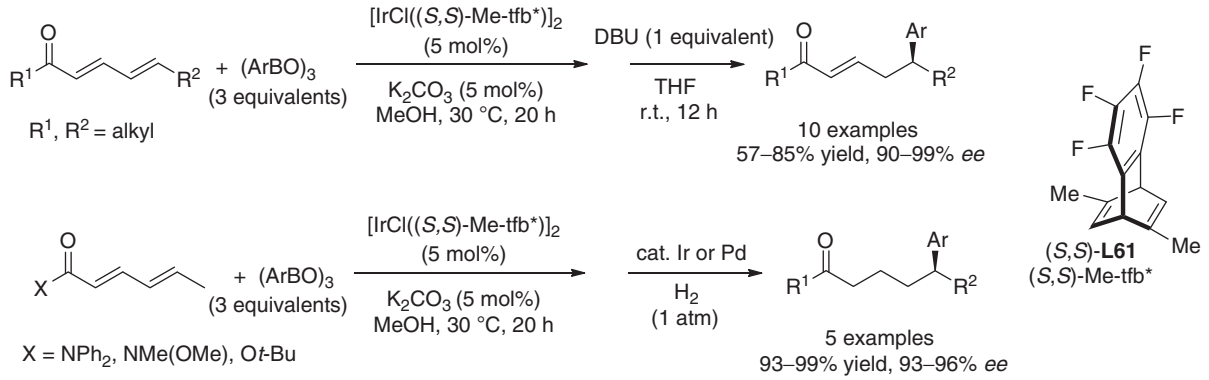


Scheme 142 Rh-promoted 1,6-addition of arylzinc reagents onto 2,4-dien-1-ones.

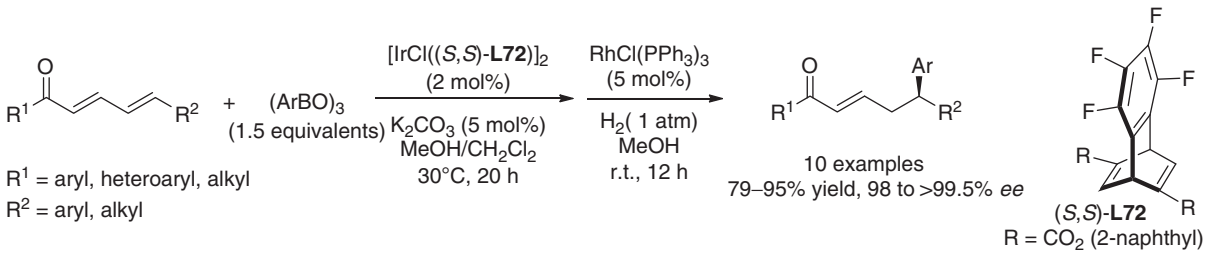
4.04.3.2 Ir-Catalyzed ACA

Although rhodium catalysts proved to be relevant in the 1,4-conjugate addition onto electron-deficient olefins, iridium complexes have showed pertinent results in the 1,6-addition methodology since the pioneering works of Hayashi and coworkers,[350] using an [Ir(μ-OH)(cod)$_2$] catalyst in the addition of arylboroxines to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds. In 2010, Nishimura and Hayashi[351] described an enantioselective version of this reaction, using an iridium/chiral diene **L71** catalyst (Scheme 143), thus affording after isomerization δ-arylated carbonyl compounds in high yields and good asymmetric induction (up to 99% *ee*). This methodology was extended to several dienamides and dienoates (Scheme 143).

However, the previously described catalytic system is only limited to dienyl ketone-bearing alkyl groups at the δ-position and displays no catalytic activity toward the reaction of δ-aryldienyl ketones. Recently, Hayashi and coworkers[352] showed that the 1,6-addition on δ-aryl-$\alpha,\beta,\gamma,\delta$-unsaturated ketones could be performed through the judicious electronic tuning of the chiral diene ligands (Scheme 144). Electron-deficient chiral dienes, and more particularly the ligand **L72**-bearing ester groups at the alkene moieties, proved to be the most efficient and the tetrafluorobenzo (tfb) moiety in the ligand was also a crucial parameter for the catalytic activity of the iridium complex. This approach gave rise to 1,6-adducts bearing a diarylmethine stereocenter in high yields and very high asymmetric induction, using arylboroxines as nucleophiles.



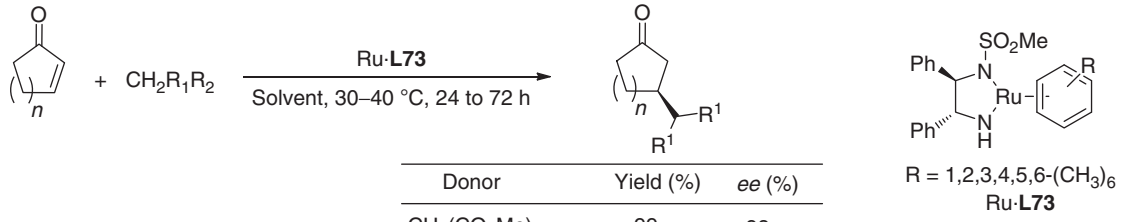
Scheme 143 Ir-promoted 1,6-addition on dienones, dienamides, and dienoates with a chiral diene ligand.



Scheme 144 Efficient methodology toward the 1,6-addition onto δ-aryl dienylketones.

4.04.3.3 Ru-Catalyzed ACA

Various chirally modified Ru catalysts have been designed and applied to asymmetric Michael additions. In 2003, Ikariya and coworkers[353] reported the reaction of five-, six-, and seven-membered unsaturated ketones with various donors, such as malonates, ketoesters, or nitroacetates, in the presence of Ru amido complexes, and more particularly Ru·**L73** catalyst (Ru(η^6-arene)(*R*,*R*)-MsDPEN, with MsDPEN = *N*-methanesulfonyl-1,2-diphenylethylenediamine) with *ee* values up to more than 99% (Scheme 145). The excellent catalyst efficiencies in terms of high reactivity and practicability (at the gram scale) were attributed to the Brønsted basicity of the amido group in the complex.



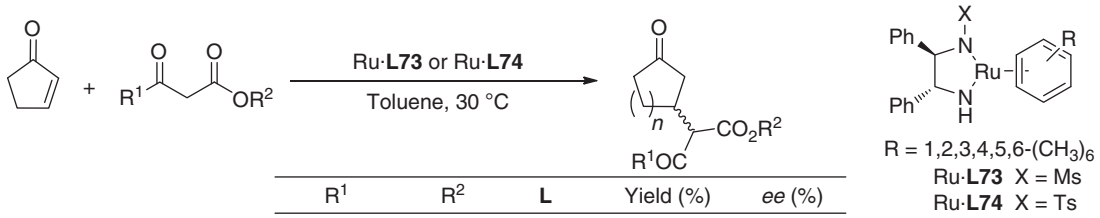
For $n = 2$

Donor	Yield (%)	*ee* (%)
$CH_2(CO_2Me)_2$	99	98
$CH_2(CO_2Et)_2$	83	>99
$CH(COMe)(CO_2Me)$	99	91
$CH_2(NO_2)(CO_2Et)$	99	92

Scheme 145 Michael additions of unsaturated ketones with various donors, catalyzed by chiral Ru amido catalysts.

However, the asymmetric induction in the addition of β-ketoesters to cyclic enones remains modest. The same authors reported later promising results in this reaction, leading to the nearly quantitative formation of 1,4-adducts with excellent *ee* values,[354] although with a 1:1 diastereoisomer ratio (Scheme 146). The structures of the used catalysts Ru·**L73** or Ru·**L74** and those of the β-ketoesters greatly influenced the sterochemical outcome of the reaction.

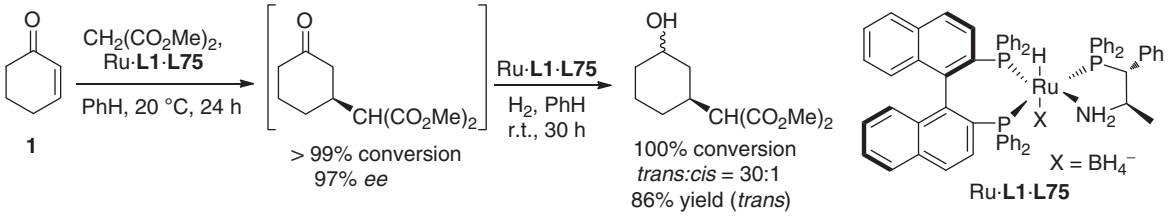
A series of novel *trans*-ruthenium hydride borohydride complexes, coordinated to optically active BINAP **L1** and aminophosphine **L75** ligands, were successfully applied to the addition of malonates to 2-cyclohexen-1-one **1** with high conversions and *ee* values up to 97% *ee*. Interestingly, the authors suggested a one-pot tandem Michael addition/hydrogenation process, using a sole



R^1	R^2	L	Yield (%)	*ee* (%)
Me	Me	**L74**	99	91
$C(CH_3)_3$	Me	**L73**	100	97
C_6H_5	Me	**L73**	91	96
C_6H_5	Et	**L73**	99	97

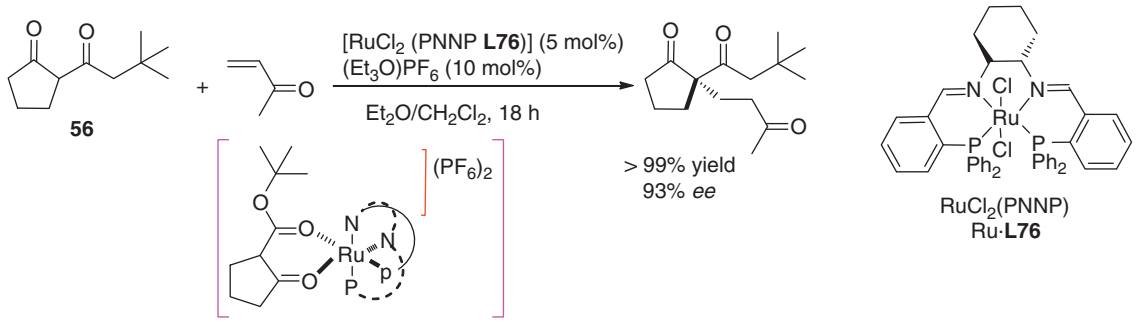
Scheme 146 Michael additions of ketoesters to cyclic enones promoted by chiral Ru amido catalysts.

catalyst, to build structures with multiple carbon stereocenters (Scheme 147). A similar Ru complex, modified by phosphinite and diamine ligands, gave quite similar results in this tandem process.[355]



Scheme 147 A one-pot tandem Michael addition/hydrogenation process catalyzed by chiral *trans*-ruthenium hydride borohydride complex.

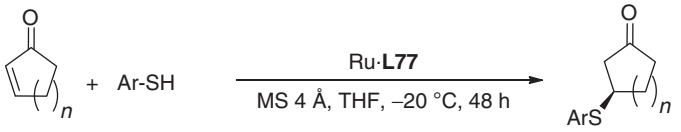
Mezzetti and coworkers[356] described chiral Lewis-acidic dicationic ruthenium/PNNP complexes of nonenolized 1,3-dicarbonyl compounds (e.g., 2-((*tert*-butoxy)carbonyl)cyclopentanone **56**), Ru·**L76** (PNNP = (1*S*,2*S*)-*N*,*N*′-bis-[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine)]. On coordination to ruthenium, the acidity of the 1,3-dicarbonyl compound is greatly enhanced. The obtained complex catalyzed the 1,4-addition of the diketone **56** to methylvinyl ketone (MVK) with up to 93% *ee*, using a CH_2Cl_2: Et_2O (1:1) solvent mixture (Scheme 148). The authors suggested that oxygen-containing cosolvents, acting as a base and a proton shuttle, promoted the deprotonation of the metal-bound *β*-keto ester and dramatically increased the catalytic activity and the asymmetric induction in the Michael addition.



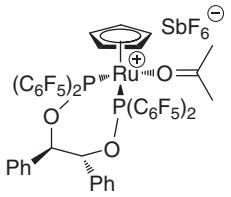
Scheme 148 Acidic Ru/PNNP chiral complexes of nonenolized 1,3-dicarbonyl compounds as pertinent catalysts for asymmetric Michael addition.

Recently, Kündig and coworkers[357] described a straightforward route toward the formation of carbon–sulfur bonds through Michael additions, taking advantage of the mild nucleophilicity of sulfur nucleophiles. To this end, they prepared ruthenium Lewis acid catalysts (Ru·**L77**) based on well-defined cationic half-sandwich complexes, bearing chiral electron-poor diphosphinite ligands. The perfluorinated aryl rings, combined with the aromatic roofs and the ligand's backbone, create a chiral binding site for the activation of *α*,*β*-unsaturated carbonyl compounds. These mild Lewis acids efficiently catalyzed the asymmetric 1,4-additions of aryl thiols to enones, affording thioethers with *ee* values up to 87% (Scheme 149). Relevant catalytic activities and selectivities were observed in spite of a complex stereocontrol and a potential catalyst inhibition.

A pertinent [Ru(phgly)$_2$(BINAP)]/C_6H_5OLi system (Ru·**L78**)[619] proved to be efficient in the ECA of HCN onto *α*,*β*-enones (Scheme 150). A variety of aryl-, heteroaryl-, or alkyl-substituted unsaturated ketones were investigated, affording the *β*-cyano



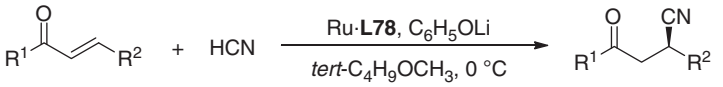
n	Ar	Yield (%)	*ee* (%)
2	Ph	82	63
2	2,6-Me-C_6H_3	95	858
1	2,6-Me-C_6H_3	95	83



(*R*,*R*)-Ru·**L77**

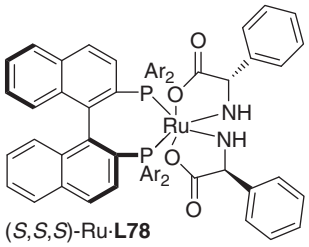
Scheme 149 Asymmetric ruthenium-catalyzed 1,4-additions of arylthiols to enones.

ketones with high regioselectivity (no detectable amount of 1,2-adduct) and asymmetric induction (up to 98% *ee*). The robust complex could be easily reused on addition of fresh C_6H_5OLi without loss of stereoselectivity.



R^1 = aryl, alkyl, heteroaryl
R^2 = alkyl

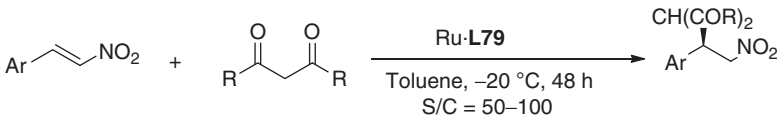
80–99% yield,
90–98% *ee*



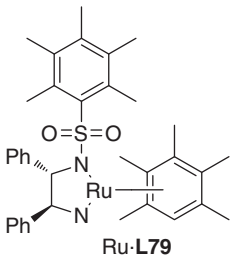
(*S*,*S*,*S*)-Ru·**L78**

Scheme 150 Asymmetric hydrocyanation of α,β-unsaturated ketones with chiral Ru catalyst.

Enantioselective Michael addition of 1,3-dicarbonyl compounds (malonates, ketoesters, diketones) onto nitroalkenes was also successfully developed in the presence of the chiral Ru amido complexes (Ru·**L79**), affording the optically active nitroalkanes with up to 98% *ee* (Scheme 151).[358] The stereochemical outcome of the conjugate addition proved to be significantly influenced by the structure of the Michael donors, and more particularly by the sterical hindrance of the group. This reaction is applicable to the synthesis of the intermediate of the chiral drug, rolipram.



Donor	Yield (%)	*ee* (%)
$CH_2(CO_2Me)_2$	99	95
$CH_2(CO_2Et)_2$	92	93
$CH(CH_3)(CO_2Me)_2$	99	97
$CH_2(CO_2Me)(CO$*i*-Pr)	97	94
$CH_2(CO_2Et)(COPh)$	96	92
$CH_2(COEt)_2$	98	97
$CH_2(CO$*i*-Pr$)_2$	99	97



Ru·**L79**

Scheme 151 Enantioselective Ru-promoted Michael addition of 1,3-dicarbonyl compounds with nitroalkenes.

4.04.4 Pd-Catalyzed Enantioselective Conjugate Addition

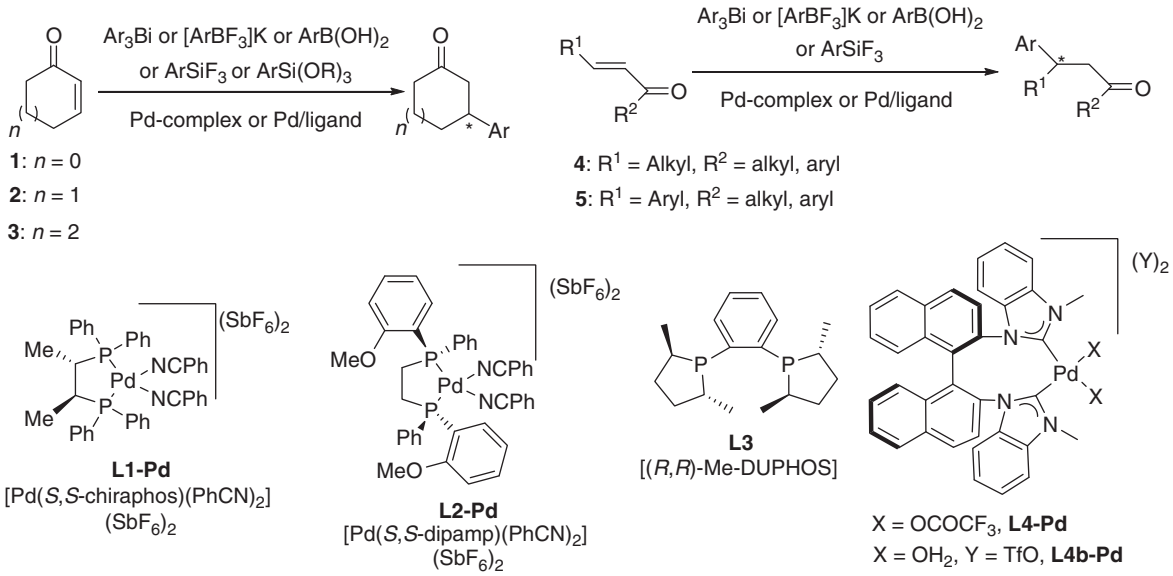
4.04.4.1 α,β-Unsaturated Enones

4.04.4.1.1 Addition of C-nucleophiles

4.04.4.1.1.1 Addition of aryl-metal and allyl-boron reagents

Because the transmetallation step of organoboron and organosilicon compounds proceeds relatively rapidly with cationic Pd(II) complexes, it is not surprising that aryltriflurosilanes,[359] arylsiloxanes,[360] potassium aryltrifluoroborates,[359,361] aryl boronic

acids,[359b,362] and triarylbismuth[359,363] were explored as nucleophiles in the Pd-catalyzed ECA on activated alkenes.[364] The most impressive results obtained from both cyclic and acyclic enones are summarized in Scheme 152 and Table 1. With cyclopentenone, the highest enantioselectivities (up to 95%) were reached by Miyaura using the Pd-chiraphos complex **L1-Pd** (entry 1). It is worth noting that Ar_3Bi, $[ArBF_3]K$, $ArSiF_3$, and $PhB(OH)_2$ led to similar results.[359,361,363] Dealing with cyclohexenone, whereas a similar behaviors was observed by the same group for the addition of various aryl groups (eight examples) using the Pd-dipamp complex **L2-Pd** (entry 2), highest *ee*s (up to 99%) were observed using a Pd/DUPHOS-catalyzed addition of both aryl siloxanes and arylboronic acids (entries 3,4).[360,362a] Using Pd complexes **L4-Pd** or **L4b-Pd** based on a bis-NHC ligand, high *ee*s (up to 97%) could be reached with a range of arylboronic acids (entry 5).[362h,365] The latter catalytic system is also the most efficient reported to date for the enantioselective 1,4-addition of aryl-metal nucleophiles on cycloheptenone (entry 6). Concerning the addition on acyclic enones, the highest *ee*s reported to date with β- alkyl enones **4** are below 90% (entry 7),[359a,361,362a–c,363] whereas more impressive results (*ee*s up to 99%) were obtained in the addition of $[ArBF_3]K$, $ArSiF_3$, and $ArB(OH)_2$ on analogous aryl enones **5** using **L1-Pd** as the catalyst (entries 8, 9).[362b,i] Interestingly, the addition of some arylboronic acids on benzalacetone and (*2E*)-1,3-diphenyl-2-propen-1-one could be run efficiently at low catalyst loading (0.05 mol%).



Scheme 152 Enantioselective Pd-catalyzed addition of Ar-metal compounds on enones.

Table 1 Enantioselective Pd-catalyzed addition of Ar-metal compounds on enones

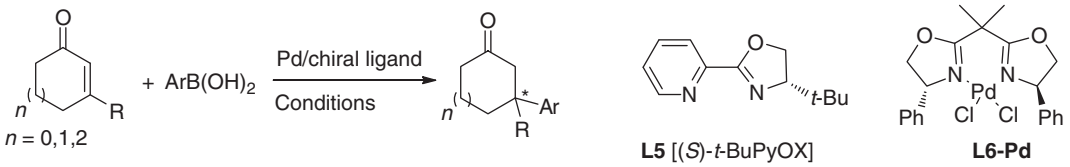
Entry	*Enone*	*Catalyst*	*Ar-M*	*Yield (%)*	ee *(%)*	*References*
1	**1**	**L1-Pd**	Ar_3Bi,[a] $[ArBF_3]K$,[b] $ArSiF_3$[c], $PhB(OH)_2$[d]	60–94	up to 95	359,361,363
2	**2**	**L2-Pd**	Ar_3Bi,[a] $[ArBF_3]K$,[b] $ArSiF_3$[c], $PhB(OH)_2$[d]	66–99	up to 96	359,361,363
3	**2**	$Pd(CH_3CN)_4(BF_4)_2$/**L3**	$ArSi(OEt)_3$[e]	60–75	up to 99	360
4	**2**	$Pd(O_2CCF_3)_2$/**L3**	$ArB(OH)_2$[f]	40 to >99	up to 99	362a
5	**2**	**L4-Pd** or **L4b-Pd**	$ArB(OH)_2$[g]	78–99	up to 97	362h,365
6	**3**	**L4-Pd** or **L4b-Pd**	$ArB(OH)_2$[g]	85–99	up to 97	362h,365
7	**4**	**L1-Pd**	Ar_3Bi,[a] $[ArBF_3]K$,[b] $ArSiF_3$[c]	22–99	up to 89	359a,361,363
8	**5**	**L1-Pd**	$[ArBF_3]K$,[b] $ArSiF_3$[c]	73–94	up to 99	359a,361
9	**5**	**L1-Pd**	$ArB(OH)_2$[d]	44–99	up to 99	362b,362i

[a]Conditions: 4 mol% Pd complex, $Cu(BF_4)_2 \cdot 6H_2O$ (0.76 equivalent), $MeOH/H_2O$, −5 °C to +10 °C.
[b]Conditions: 3 mol% catalyst, $MeOH/H_2O$, −15 °C to +5 °C.
[c]Conditions: 3 mol% catalyst, ZnF_2 (1 equivalent), $MeOH/H_2O$, 0 °C or 5 °C.
[d]Conditions: 0.5 or 1 mol% Pd complex, silver salt additive (0–0.2 equivalent), acetone/H_2O, 0 °C or 25 °C.
[e]Conditions: 5 mol% Pd, 5.5 mol% ligand, ZnF_2 (1 equivalent), dioxane/H_2O, 50 °C.
[f]Conditions: 5 mol% Pd, 5.5 mol% ligand, THF/H_2O, 50 °C.
[g]Conditions: 3 mol% Pd complex, KOH, THF, or dioxane/H_2O, r.t.

Works dedicated to illustrate the potential of the **L1-Pd**-catalyzed 1,4-addition of arylboronic acids to β-arylenones in synthesis were reported by Miyaura. First, a series (14 examples) of 1-aryl-1*H*-indenes were synthesized in high *ee*s (up to 97%) and yields

through a tandem process involving an enantioselective 1,4-addition of arylboronic acids on β-(2-acylaryl)enones followed by an intramolecular aldol-dehydration sequence.[366] Besides, **L1-Pd**-catalyzed 1,4-addition of arylboronic acids to (2-hydroxyaryl) enones followed by Baeyer–Villiger oxidation on the crude product afforded 4-aryldihydrocoumarins in high *ee*s (up to 98%) and good yields.[362i]

Recently, the asymmetric formation of quaternary centers was explored by Stoltz using pyridinooxazoline ligand **L5** (Scheme 153).[362e]

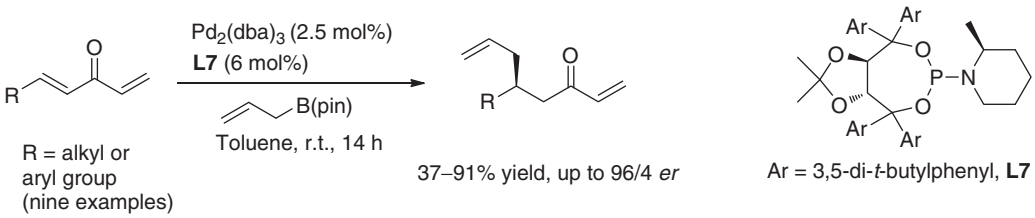


R = Me, Et, *n*-Bu, Bn, *i*-Pr, *c*-pr, *c*-hex, $(CH_2)_3OBn$	15 $ArB(OH)_2$ reagents	$Pd(OCOCF_3)_2$ (5 mol%) **L5** (6 mol%) $(CH_2)_2Cl_2$, 40–80 °C, 12–24 h	40–99% yield, 69–96% *ee*
R = Me, Et	9 $ArB(OH)_2$ reagents	**L6-Pd** (8 mol%) $AgSbF_6$ (20 mol%) MeOH/H_2O, 40–60 °C, 24–40 h	30–98% yield, 93 to >99% *ee*

Scheme 153 Formation of quaternary centers by Pd-catalyzed enantioselective conjugate addition of $ArB(OH)_2$ on cyclic enones.

Either 3-methylyclohexen-2-one was reacted with a wide range of $ArB(OH)_2$, or when $PhB(OH)_2$ was added to various β-substituted cyclic enones, the adducts were isolated in most cases in very good *ee*s (typically 85–95%) and good to very high yields. The lowest *ee*s were obtained with electroenriched aryl groups. Later, de Vries and Minnaard reached better enantioselectivities (up to >99%) using 8 mol% of PhBOX-based complex **L6-Pd** (Scheme 153) along with 20 mol% of $AgSbF_6$ as dehalogenating salt.[367] The behavior of acyclic enones was also explored but poor results were observed.

The conjugate addition of allylB(pin) on β-substituted acyclic enones was investigated by Morken.[368] The most valuable results were obtained using ketones exhibiting a vinyl and an alkylidene (or arylidene) substituent. Using a Pd/phosphoramidite **L7** catalytic system, the reaction was fully regioselective on both β-alkyl- and β-aryl-substituted substrates and the products were isolated in good enantioselectivities (Scheme 154).[368b]



Scheme 154 Enantioselective Pd/**L7**-catalyzed addition of allylB(pin) on acyclic enones.

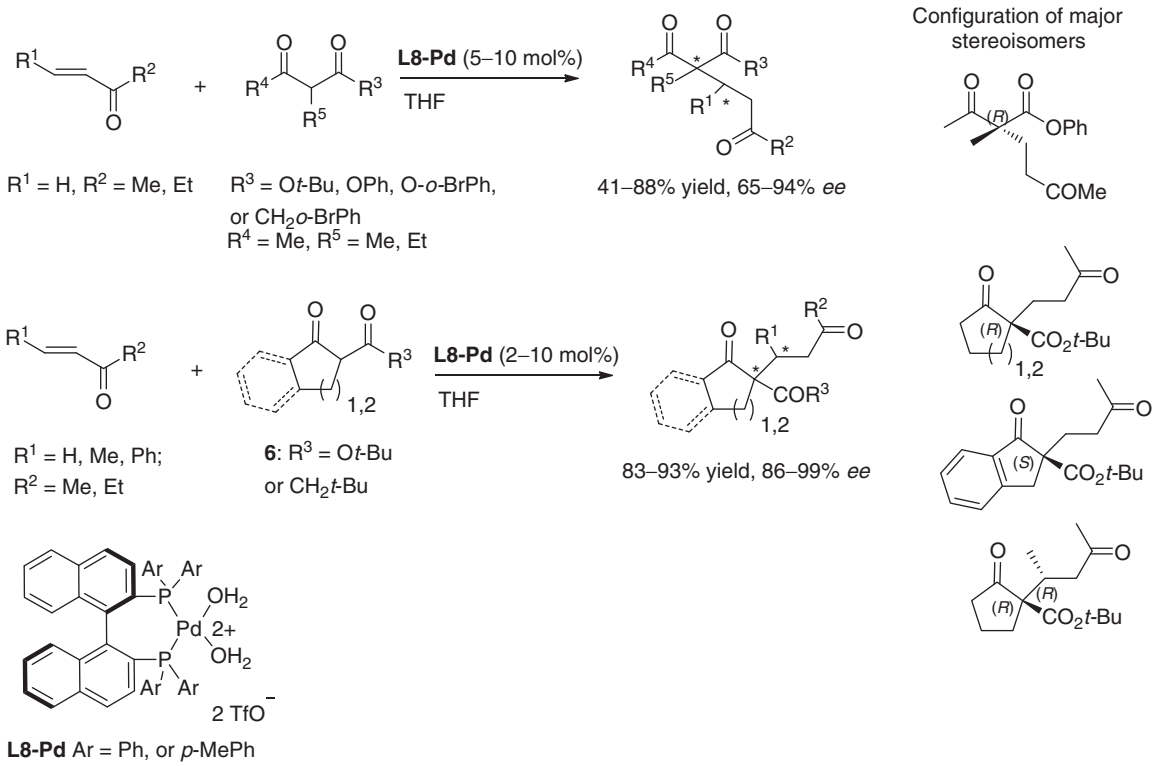
4.04.4.1.1.2 Addition of β-dicarbonyl compounds and related nucleophiles

Pioneering works in the area, reported in 2000, concerned the conjugate addition of α-cyanoester nucleophiles on methylvinyl ketone, but only moderate *ee*s were achieved.[369] Later, Sodeoka explored the addition of both cyclic and acyclic β-keto esters and β-diketones on acyclic enones, using chiral palladium aqua complex **L8-Pd**.[370] Owing to basic properties of the Pd-OH moiety, intermediate chiral palladium enolates are formed which add on enones to give quaternary chiral center products in good yields and good to very high *ee*s (Scheme 155). Interestingly, some examples of reaction were tested in water[370b] and ionic liquids[371] as solvents and this led to only a low decrease (3–4%) in the enantioselectivities compared to those observed in THF. When the same catalytic system was applied to the addition of a cyclic β-ketoester to cyclohexenone and cyclopentenone, two diastereoisomers were obtained in a 1.2–1.6/1 ratio.[370c]

The addition of a cyclic β-keto ester on MVK was also investigated using a bis NHC-based Pd^{2+} aqua complex but lower *ee*s (at most 71%) were reached.[372] α-Methyl α-cyano esters were also tested as nucleophiles using a pincer Pd complex as catalyst, but *ee*s were at most 83%.[373]

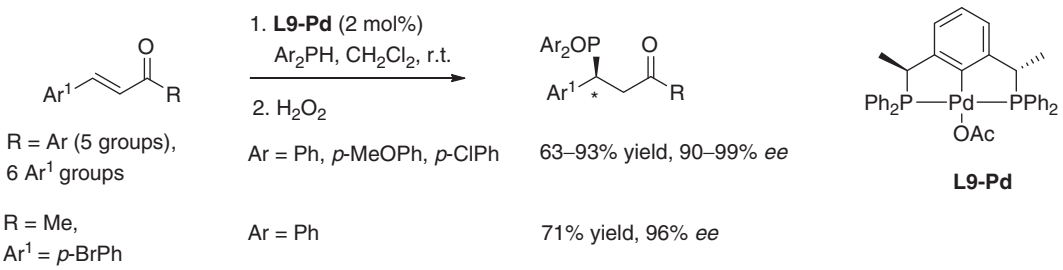
4.04.4.1.2 Addition of phosphorus nucleophiles

The asymmetric metal-catalyzed hydrophosphination of olefins is a quite challenging transformation and this may explain that the first example in Pd chemistry was reported only in 2010. Using 2 mol% of PCP-pincer Pd complex **L9-Pd** as catalyst, Duan studied



Scheme 155 Enantioselective **L8-Pd**-catalyzed conjugate addition of β-dicarbonyl compounds on acyclic enones.

the asymmetric addition of electron-poor and -rich diarylphosphines on a series of chalcones and also on a cinnamyl methyl ketone. After hydrogen peroxide oxidation, phosphine oxides were obtained in excellent *ee*s (up to 99%) and satisfactory yields (Scheme 156).[374]

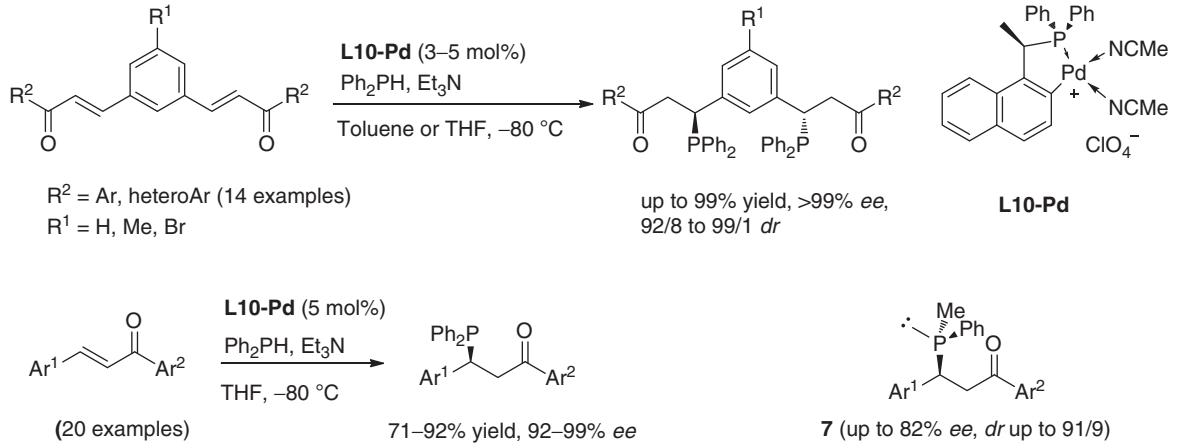


Scheme 156 Enantioselective **L9-Pd**-catalyzed hydrophosphination of acyclic enones.

Among the next developments in this area,[375] the most impressive progresses were reported by Leung, using C-P palladacycle **L10-Pd** as catalyst. First, the double hydrophosphination of symmetrical substrates bearing two enone groups was investigated. Sixteen bis-enones having aromatic or heteroaromatic substituents were converted to bis-phosphines with both excellent dia- and enantioselectivities (>99% *ee*; Scheme 157).[375c] The same catalytic system was used for the hydrophosphination of numerous chalcones. The free chiral phosphines were obtained in good yields and excellent *ee*s (up to 99%). Moreover, the diastereo- and enantioselective addition of racemic methylphenylphosphane was also performed using similar conditions, leading to the creation of both C and P chiral centers. Products **7** were generally isolated in moderate to good *dr* and interesting *ee*s, ranging from 42% to 82% (Scheme 157).[375d]

4.04.4.1.3 Addition of silicon nucleophiles

The enantioselective-catalyzed 1,4-addition of unsymmetric disilane on acyclic enones was reported as early as 1988, with Pd[(*R*)-BINAP]Cl_2 as the catalyst.[376] The resulting disilylated adducts were transformed into chiral β-silyl ketones through successive treatments with MeLi and diluted HCl. However, the latter were isolated in variable *ee*s (47–92%).

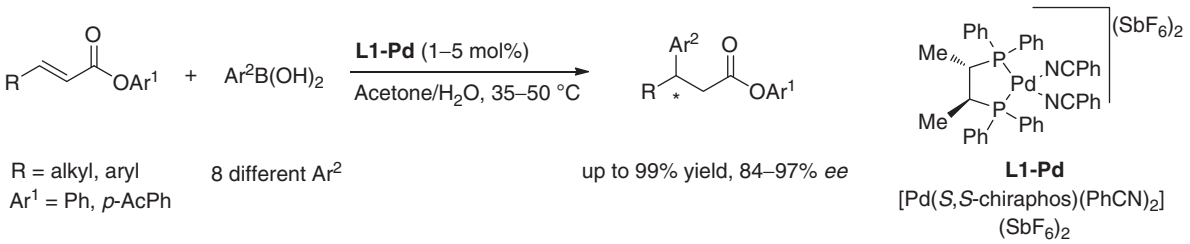


Scheme 157 Enantioselective **L10-Pd**-catalyzed hydrophosphination of acyclic enones.

4.04.4.2 Unsaturated Esters, Lactones, Thioesters

4.04.4.2.1 Addition of C-nucleophiles

The conjugate addition of various aryl boronic acids on both *β*-alkyl- and *β*-aryl unsaturated aryl esters was studied using **L1-Pd** as the catalyst.[377] The adducts were isolated in usually good to excellent *ee*s (up to 97%) and good yields (Scheme 158).



Scheme 158 Enantioselective **L1**-catalyzed conjugate addition of $ArB(OH)_2$ on unsaturated esters.

It must be noted that the major pathway was a Heck reaction instead of a 1,4-conjugate addition when alkyl esters were used instead of aryl esters. Besides, the conditions were successfully extended to a tandem 1,4-addition/aldol cyclization furnishing highly enantioenriched arylindenes.

The reactivity of lactones was tested under some of the conditions described in Section 4.04.4.1.1.1 for enones. For instance, the **L3** (see Scheme 152)-catalyzed addition of triphenylboroxine on 5,6-dihydro-2*H*-pyran-2-one afforded the adduct in 94% *ee*,[362a] whereas the **L6Pd**-catalyzed (see Scheme 153) reaction of phenyl boronic acid on 4-methyl-dihydropyranone led to the quaternary chiral center product in 88% *ee*.[367] Finally, an enantioselective Pd/Tol-BINAP-catalyzed Friedel–Crafts alkylation involving indoles and an unsaturated thioester was described.[378] However, the enantioselectivity was fairly good (70–86% *ee*), whereas the isolated yields varied greatly, ranging from only 20% to 80%.

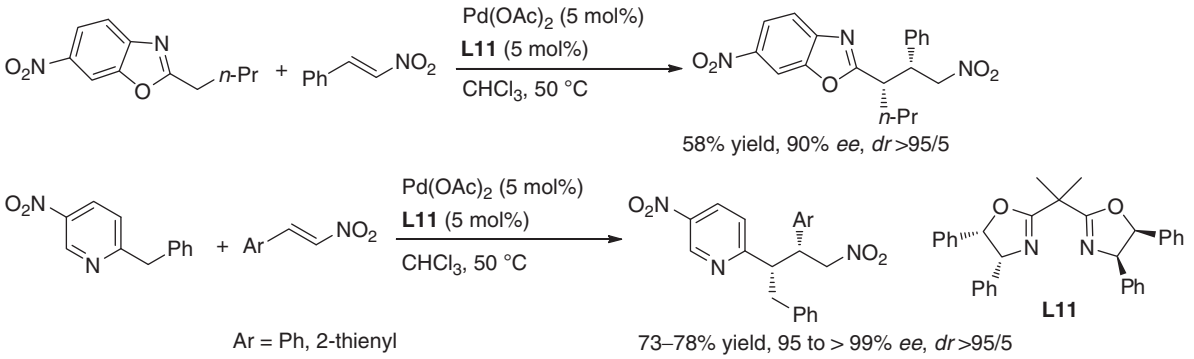
4.04.4.2.2 Addition of boron and phosphorus-nucleophiles

The addition of bis(pinacolato)diboron on few crotonoates was reported using a $Pd_2(dba)_3$ as metal source and (*R*)-(*S*)Josiphos as chiral ligand. The *β*-boryl esters were obtained in good *ee*s (up to 91%); however, a Ni-catalyzed version under similar conditions which is described in the same paper showed better efficiency in term of enantioselection (see Section 4.04.5.2).[379]

Leung applied catalyst **L10-Pd** (see Scheme 157), also evaluated in the hydrophosphination of unsaturated ketones (see Section 4.04.4.1.2), to *β*-substituted ethyl methylidene malonates.[380] High *ee*s (up to 99%) were reached with substrates having (hetero)aromatic- or cinnamyl group in the *β*-position, whereas poorer results were observed with those bearing a methyl or a methoxy substituent.

4.04.4.3 Nitroolefins

Noteworthy results were reported in the addition of 2-butyl-6-nitro-1,3-benzoxazole and 2-benzyl-5-nitropyridine to nitroolefins using $Pd(OAc)_2$ modified by bis(oxazoline) **L11**. As depicted in Scheme 159, the products were isolated in both remarkable *ee*s (up to 99%) and diastereoselectivities.[381]



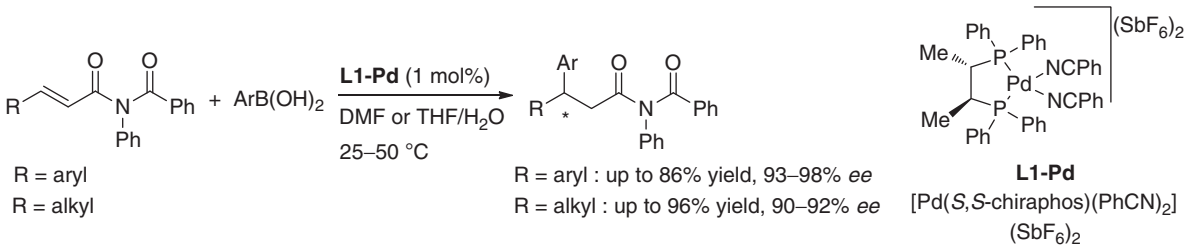
Scheme 159 Enantioselective Pd/**L11**-catalyzed 1,4-addition on nitroalkenes.

The Friedel–Crafts reaction of pyrroles and nitroolefins using a chiral trimetallic Pd-Sm-Pd complex was also described but with somewhat varying enantioselectivities.[382]

4.04.4.4 Unsaturated Lactames, Imides and *N*-Alkenoyl-Carbamates, -Oxazolidinones, -Pyrrolidinones

4.04.4.4.1 Addition of C-nucleophiles

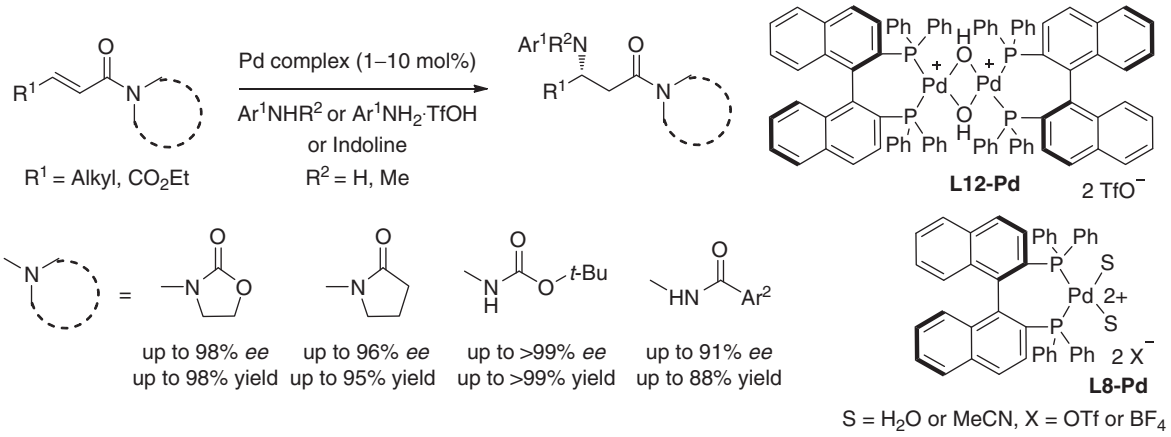
The addition of $PhSi(OEt)_3$ on one example of unsaturated lactame was also tested under the conditions described in Section 4.04.4.1.1.1 for enones (see Scheme 152 and Table 1, entry 3), giving 1-Cbz-4-phenyl-2-piperidinone in 94% *ee*.[360] The **L1-Pd**-catalyzed addition of aryl boronic acids on various β-aryl and -alkyl substituted α,β-unsaturated imides was reported by Miyaura.[383] Higher *ee*s were reached with Michael acceptors bearing aryl substituents in the β-position (93–98%) than with alkyl-substituted analogs (Scheme 160). The conditions were extended to (*N*-methyl)maleimide which furnished the adducts in high yields and 90% *ee*.



Scheme 160 Enantioselective **L1**-catalyzed conjugate addition of aryl boronic acids on unsaturated imines.

4.04.4.4.2 Addition of nitrogen nucleophiles

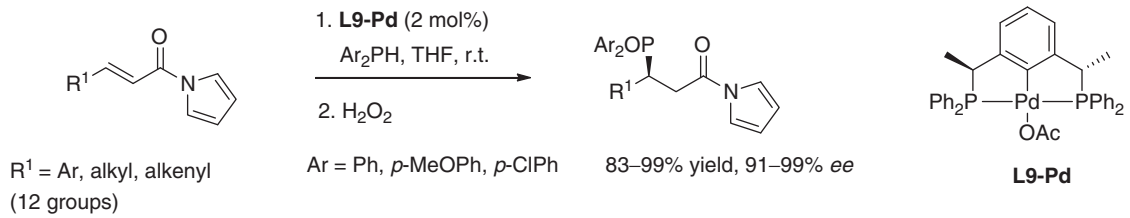
The enantioselective Pd-catalyzed addition of arylamines to *N*-alkenoyl-carbamates,[384] *N*-alkenoyl-oxazolidinones,[385] *N*-alkenoyl-pyrrolidinones,[385d] and unsaturated *N*-imides[384b,386] was investigated using cationic Pd complexes **L8-Pd** and **L12-Pd** (Scheme 161). Concerning *N*-alkenoyl-oxazolidinones, particularly interesting results were reported by Sodeoka, using 0.2–4 mol% of **L12-Pd** and triflate salts of primary arylamines. The expected adducts were isolated in high *ee*s (85–98%) and most often in good yields. Interestingly, electron-rich and -poor arylamines led to similar enantioselectivities. When addition of the benzyl-amine salt was considered, little lower *ee*s (80–86%) were observed.[385b] Good to excellent *ee*s were reached for the addition of primary arylamines (83–96%) and indoline (87%) on fumaryl pyrrolidinones ($R^1 = CO_2Et$) employing 5 mol% of **L8-Pd** ($X = BF_4$).[385d] The addition of various primary aryl amines on *N*-alkenoyl-carbamates was also explored, using **L8-Pd** (X=TfO) either as an isolated complex or prepared *in situ*.[384a,b] The reaction appears to be highly reagent-dependent because remarkable *ee*s (up to >99%) were only achieved with electron-poor amines and aniline, whereas the reactivity was poorer with Et or *n*-Pr (R^1)-substituted electrophiles than with the crotonoyl analog ($R^1 = Me$). The same group extended the conditions to unsaturated imides.[384b,386a] This time, the catalytic systems seemed more tolerant of the electronic properties of the aryl amine and the *ee*s ranged from only 52% to 91%. Careful mechanistic investigations were undertaken dealing with the case of unsaturated imides which led to a modified protocol allowing to increase the enantioselectivities in the additions of *p*-methoxyaniline on an unsaturated imide (86% *ee*) and also an *N*-alkenoyl-carbamate (73% *ee*).[386b] The addition of anilines to *N*-alkenoyl-carbamates was successfully applied to the asymmetric synthesis of torcetrapib.[387]



Scheme 161 Enantioselective Pd-catalyzed conjugate addition of arylamines on *N*-alkenoyl-carbamates, *N*-alkenoyl-oxazolidinones, *N*-alkenoyl-pyrrolidinones, and unsaturated *N*-imides.

4.04.4.4.3 Addition of phosphorus nucleophiles

Duan examined the ECA of diarylphosphines on *α,β*-unsaturated *N*-acylpyrroles under similar conditions to those he used with enones (see Section 4.04.4.1.2). Starting from a wide range of electrophiles bearing aryl-, alkenyl, or alkyl-substituents in the *β*-position, the conjugate addition followed by a H_2O_2-mediated oxidation gave the chiral phosphine oxides in very high *ee*s (usually 94–99%) and most often in excellent yields (Scheme 162).[388]



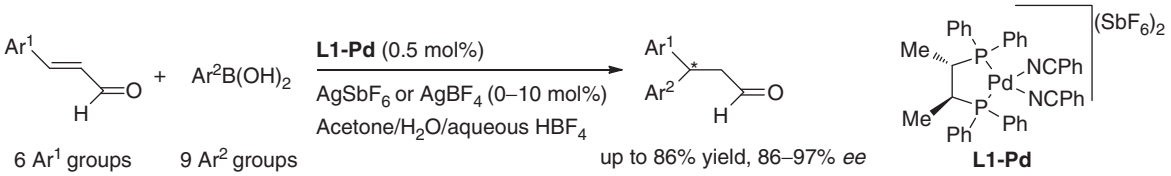
Scheme 162 **L9-Pd**-catalyzed addition of diarylphosphines to unsaturated *N*-acylpyrroles.

4.04.4.5 Unsaturated Aldehydes

4.04.4.5.1 Addition of C-nucleophiles

The addition of *β*-ketoesters **6** on acrolein and crotonaldehyde was explored by Sodeoka under similar conditions to those used with enones and depicted in Scheme 155 (see Section 4.04.4.1.1.2). The adducts were isolated as corresponding dimethyl acetal derivatives in good to excellent *ee*s (80–99%).[370c]

Applying close conditions to those he used for enones, Miyaura investigated the **L1-Pd**-catalyzed conjugate addition of aryl-boronic acids to *β*-arylenals (Scheme 163).[389] Aside from the most bulky ones, various EDG-substituted arylboronic acids gave bis-arylaldehydes in good to high *ee*s (up to 97%). Enal-bearing aliphatic substituents in the *β*-position were also examined but they led to more moderate *ee*s (67–70%). Interestingly, the methodology was successfully applied to the synthesis of (+)-(*R*)-CDP840.

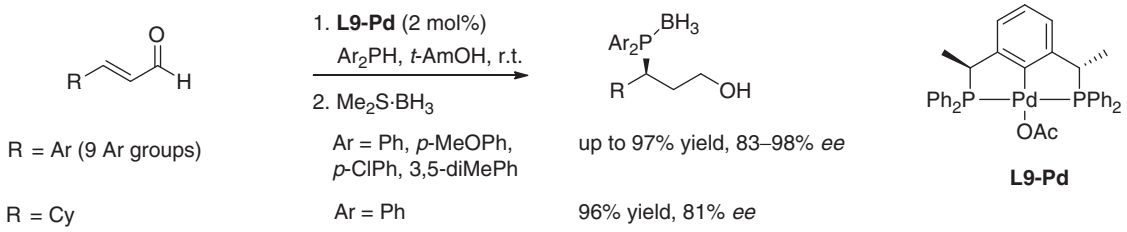


Scheme 163 Enantioselective **L1-Pd**-catalyzed 1,4-addition of arylboronic acids on *β*-arylenals.

4.04.4.5.2 Addition of phosphorus nucleophiles

Duan studied the ECA of diarylphosphines on enals with the same chiral Pd-complex that was used for the addition of Ar_2PH on enones and unsaturated *N*-acylpyroles (see Sections 4.04.4.1.2 and 4.04.4.4.3). After treatment of the adducts with $BH_3{\cdot}SMe_2$,

hydroxy phosphine-boranes were isolated in good to high *ee*s, β-aryl-α,β-unsaturated aldehydes affording better enantioselectivities than β-alkyl counterparts (Scheme 164).[390] It is worth underlining that catalyst loading could be decreased to 0.05 mol% without any significant drop in enantioselectivity. Moreover, successful extension to the synthesis of a bisphosphine, starting from a substrate bearing two enal moieties, is also described.



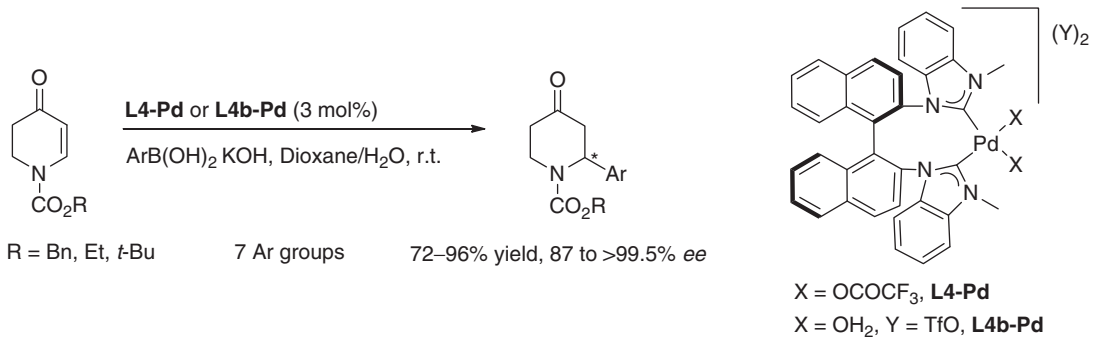
Scheme 164 Enantioselective **L9-Pd**-catalyzed addition of diarylphosphines on enals.

4.04.4.6 Miscellaneous Michael Acceptors (2,3-Dihydro-4-Pyridones, Unsaturated Ketophosphonates, Unsaturated Ketoesters)

4.04.4.6.1 Addition of C-nucleophiles

4.04.4.6.1.1 Addition of aryl-boron and aryl-silicon reagents

Although Pd/(*R,R*)-Me-DUPHOS-catalyzed addition of both $PhSi(OEt)_3$ and $PhB(OH)_2$ on *N*-(benzyloxycarbonyl)-2,3-dihydro-4-pyridone led to a remarkable enantioselectivity (99% *ee*),[360,362a] a wider scope regarding both aryl boronic acids and dihydropyridones was reported later by Shi using **L4-Pd** or **L4b-Pd** complexes as catalysts (Scheme 165).[365] Regardless of the arylboronic acid and the nature of the nitrogen substituent, the products were isolated in usually very good yields and excellent *ee*s, ranging from 96% to >99.5% with the most selective complex.



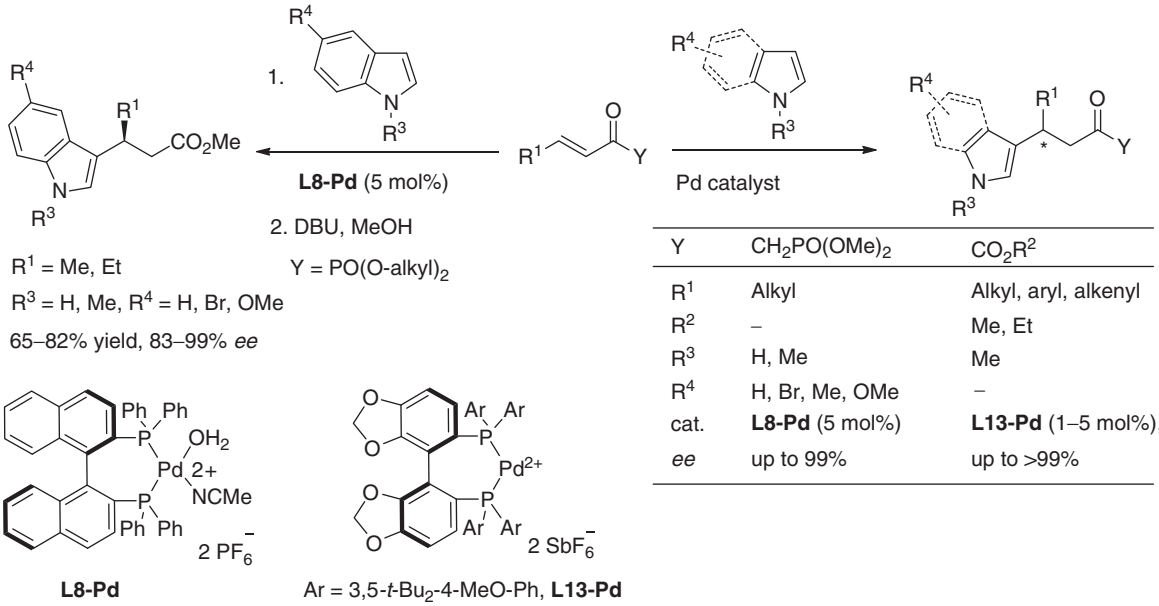
Scheme 165 Enantioselective **L4/L4b**-catalyzed conjugate addition of aryl boronic acids on dihydropyridones.

4.04.4.6.1.2 Friedel–Crafts reactions

As unsaturated esters appear inadequately reactive in catalytic enantioselective Friedel–Crafts reactions, more activated derivatives, such as unsaturated keto phosphonates and unsaturated ketoesters, were tested (Scheme 166). Using 5 mol% of BINAP-based cationic complex **L8-Pd**, some indoles were reacted with γ-alkyl-substituted β,γ-unsaturated α-ketophosphonates [Y=PO(O-alkyl)$_2$]. The adducts were converted into the corresponding more stable methyl esters which were obtained in good yields and good to excellent *ee*s (83–99%), with the lowest enantioselectivities being observed with *N*-methyl indoles. Moreover, γ-phenyl-substituted analogs gave poor results.[391] The same group examined also the behavior of γ,δ-unsaturated β-ketophosphonates [Y=$CH_2PO(OMe)_2$], using the same catalyst. Provided that δ-alkyl-substituted Michael acceptors were used, a highly enantioselective alkylation was observed with both indoles and pyrroles (85–99% *ee*).[392] β,γ-Unsaturated α-ketoesters (Y=CO_2R^2) were also evaluated as Michael acceptors toward indoles and *N*-methyl pyrrole using 1–5 mol% of **L13-Pd** as catalyst. Although only moderate to good enantioselectivities were reached with *N*-methyl indole, the reaction of *N*-methyl pyrrole, at −78 °C, with electrophiles bearing a range of substituents in the γ-position, including an alkenyl group, furnished the 1,4-adducts in very high *ee*s (up to >99%) and most often very good yields (60–97%).[393]

4.04.4.6.2 Addition of nitrogen nucleophiles

The addition of aliphatic secondary amines on methacrylonitrile, using a Pd(II)/PCP complex as the catalyst, was examined by Togni. However, only moderate *ee*s were attained (at best 75%).[394]



Y	$CH_2PO(OMe)_2$	CO_2R^2
R^1	Alkyl	Alkyl, aryl, alkenyl
R^2	–	Me, Et
R^3	H, Me	Me
R^4	H, Br, Me, OMe	–
cat.	**L8-Pd** (5 mol%)	**L13-Pd** (1–5 mol%),
ee	up to 99%	up to >99%

Scheme 166 Enantioselective Pd-catalyzed Friedel–Crafts reaction on unsaturated keto phosphonates and unsaturated ketoesters.

4.04.4.7 Extended Michael Acceptors

Extended (dienic) systems were scarcely tested as substrates in the works presented in the previous sections (see Sections 4.04.4.4.3 and 4.04.4.6.2). The formation of 1,6-adducts was never mentioned and only 1,4-adducts were isolated.

4.04.5 Ni-Catalyzed Enantioselective Conjugate Addition

4.04.5.1 α,β-Unsaturated Enones

4.04.5.1.1 Addition of C-nucleophiles

4.04.5.1.1.1 Addition of dialkylzinc reagents

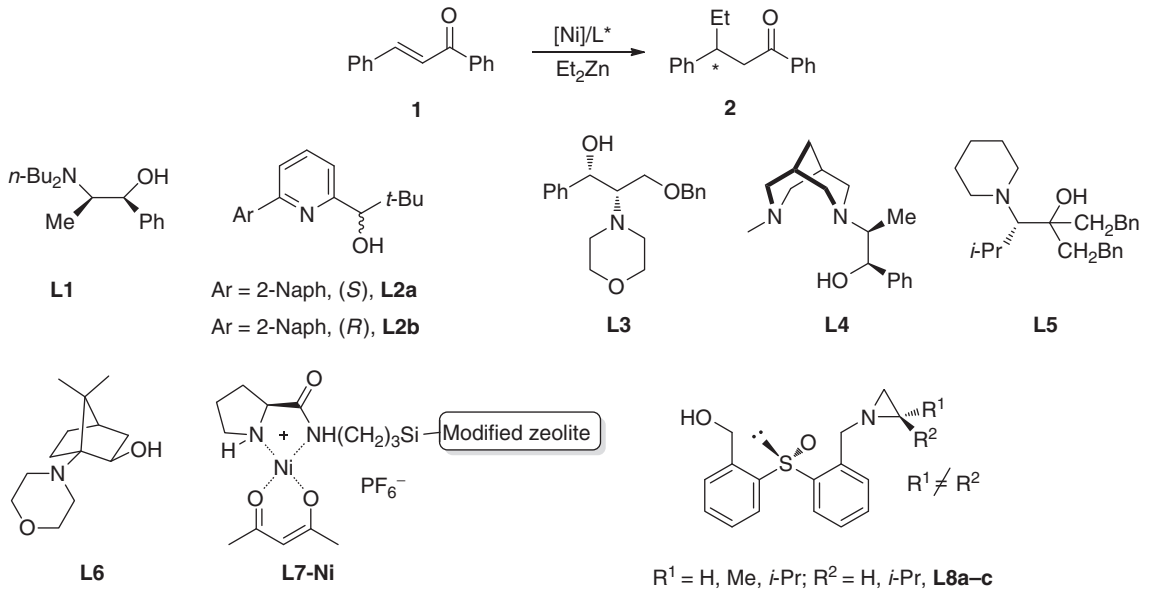
A large majority of works related to Ni-catalyzed ACA on enones investigated the use of dialkylzinc, and most often diethylzinc, as the nucleophile. It is interesting to compare the various catalytic systems tested on the base of their efficiency for the addition of diethylzinc to chalcone **1**, as this acyclic enone is usually used as the reference substrate (Scheme 167). Many ligands were evaluated as early as 1988,[395] but most of them gave enantioselectivities unsatisfactory for applications in synthesis. In Table 2, only catalytic systems yielding product **2** with *ee*s above 85% will be presented.

The first valuable enantioselectivity for the addition of Et_2Zn on chalcone **1** (90%) was reported in 1989 by Soai et al. using β-aminoalcol **L1** as the ligand in the presence of an achiral coligand (entry 1).[396] A reaction was also attempted with *n*-Bu_2Zn but a lower *ee* was obtained (74%). Generally, reactivity of dialkylzinc reagents other than Et_2Zn was rarely explored and the best *ee*s reported to date with Me_2Zn an *n*-Bu_2Zn are respectively only 75% and 82%.[395u,403] Concerning the addition of Et_2Zn, the most enantioselective catalytic systems were reported by Kiełbasiński et al. in 2010 and by Uang et al. in 2012 using respectively tridentate ligands **L8a–c** and β-amino alcohol **L6** (entries 7–8).[402,403] Indeed, *ee*s up to 93% could be reached in the presence of loadings of chiral ligands lower than those usually used in the Ni-catalyzed ACA. Finally, the mechanistic aspects of the Ni-catalyzed ACA were scarcely discussed,[395k,397b,400] but it is worth noting that moderate to significant positive NLEs were observed in some cases.[395u,397]

Some of the conditions evaluated with substrate **1** were also extended to substituted chalcones (Scheme 168) and a selection of the most interesting results is presented in Table 3.

No clear-cut trend could be drawn about the possible influence of electronic/steric factors of the substituants in the aryl group. The different catalytic systems led to somewhat contradictory results dealing with the influence of the nature of both aryl groups on the enantioselectivity. Nevertheless, it can be noted from results reported in Tables 2 and 3 that the most enantioselective catalytic system for a given substituted chalcone gives an *ee* close to the highest one reached for chalcone **1** (93%).

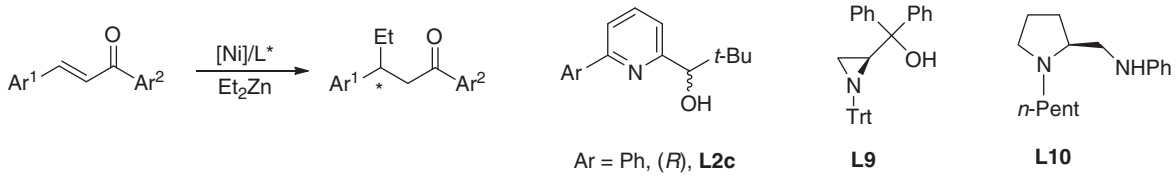
Although many results have been reported with chalcones, the addition on acyclic enones bearing an alkyl group at either position has not been much exemplified. Moreover, enantioselectivities were usually low to moderate,[395b,c,t,v,397b,403] the only exception being the addition of Et_2Zn on benzalacetone **3** in the presence of supported Ni catalyst **L7-Ni**, (Scheme 169) where the expected adduct **4** was isolated in 95% *ee*.[398]



Scheme 167 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on chalcone.

Table 2 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on chalcone

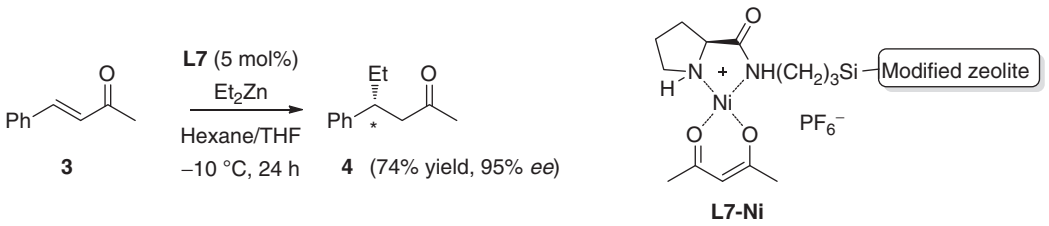
Entry	*Ni (mol%)*	*Ligand (mol%)*	*Conditions*	*Yield (%)*	ee *(%)*	*Configuration*	*References*
1	$Ni(acac)_2$ (7)	**L1** (17)	2,2′-Bipyridyl (7 mol%), CH_3CN, –30 °C	47	90	*R*	396
2	$Ni(acac)_2$ (1)	**L2a/L2b** (20–22)	CH_3CN, –30 °C	84	86	*R/S*	397
3	**L7-Ni** (5)	Isolated Ni complex	Hex/THF, –10 °C	80	91	*R*	398
4	$Ni(acac)_2$ (1)	**L3** (20)	MS 3Å, CH_3CN, –40° to –35 °C	64	88	*R*	399
5	$Ni(acac)_2$ (1)	**L4** (20)	2,2′-Bipyridyl (1 mol%), CH_3CN, –30 °C	86	85	*S*	400
6	$Ni(acac)_2$ (1.5)	**L5** (20)	C_2H_5CN, –30 °C	71	91	*S*	401
7	$Ni(acac)_2$ (7)	**L8a–c** (11)	Toluene, –20 °C, 1 h → r.t. o.n.	91–95	91–93	*R/S*	402
8	$Ni(acac)_2$ (0.5)	**L6** (12.5)	C_2H_5CN, –60 °C	88	93	*S*	403



Scheme 168 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on substituted chalcones.

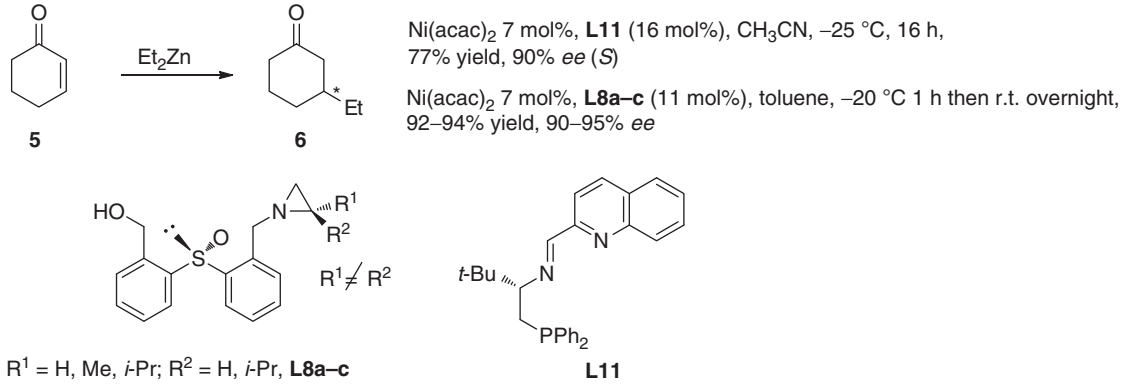
Table 3 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on substituted chalcones

Entry	*Ar^1*	*Ar^2*	*Ni (mol%)*	*Ligand (mol%)*	*Yield (%)*	*ee (%)*	*Configuration*	*References*
1	4-MeOPh	Ph	$Ni(acac)_2$ (1.5)	**L5** (20)	65	92	*S*	401
2	4-MePh	Ph	$Ni(acac)_2$ (0.5)	**L6** (12.5)	81	89	*S*	403
3	4-BrPh	Ph	$Ni(acac)_2$ (0.5)	**L6** (12.5)	76	90	*S*	403
4	4-ClPh	Ph	$Ni(acac)_2$ (1.0)	**L2c** (20)	78	90	–	397b
5	4-FPh	Ph	$Ni(acac)_2$ (0.5)	**L6** (12.5)	87	89	*S*	403
6	4-F_3C-Ph	Ph	$Ni(acac)_2$ (0.5)	**L6** (12.5)	76	91	*S*	403
7	3-ClPh	Ph	$Ni(acac)_2$ (0.5)	**L6** (12.5)	83	92	*S*	403
8	Ph	4-MeOPh	$NiCl_2$ (1.5)	**L10** (30)	50	89	*S*	395h
9	Ph	3-MeOPh	$Ni(acac)_2$ (9)	**L9** (10)	67	93	*R*	395n



Scheme 169 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on benzalacetone.

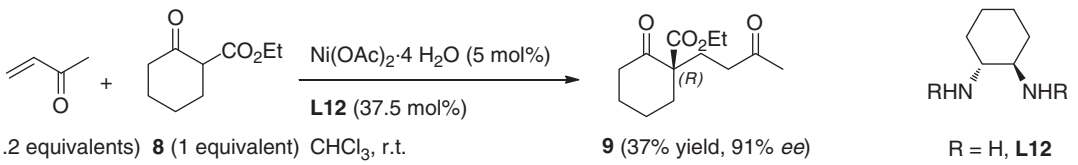
The reactivity of cyclic enones has also been poorly investigated;[395k,u,397b] however, good *ee*s were reported for the addition of Et_2Zn on cyclohexenone **5** in 2008 and 2010 by Hayashi et al. and Kiełbasiński et al., respectively (Scheme 170).[61,402]



Scheme 170 Enantioselective Ni-catalyzed conjugate addition of Et_2Zn on cyclohexenone.

4.04.5.1.1.2 Addition of miscellaneous C-nucleophiles

Of all the types of nucleophiles, the ones that have been the most intensively explored in the Ni-catalyzed enantioselective conjugate addition on enones are dialkylzinc reagents. Among other families, the reaction of active hydrogen compounds (Michael addition) has been studied as early as the beginning of the 1990s. Pioneering works were reported in 1991 by Botteghi and Boga, who investigated the addition of nitromethane on chalcone using bidentate ligands derived from Pro, but only moderate *ee*s (up to 60.9%) were obtained.[404] As depicted in Scheme 171, a good *ee* (91%) was obtained by Christoffers in the Ni-catalyzed addition of β-ketoester **8** on MVK **7** using a substoechiometric amount of chiral diamine **L12** as the ligand.[405] Interestingly, this reaction does not require anhydrous and anaerobic conditions, but a moderate yield and a narrow scope are its main drawbacks. Indeed, more moderate *ee*s were observed with cyclic 5- and 7-member analogs and also analogous β-diketones.

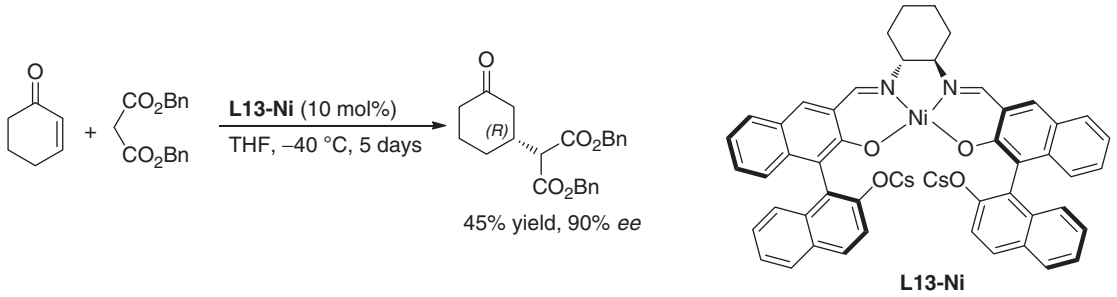


Scheme 171 Enantioselective Ni/**L12**-catalyzed addition of β-ketoester **8** on MVK.

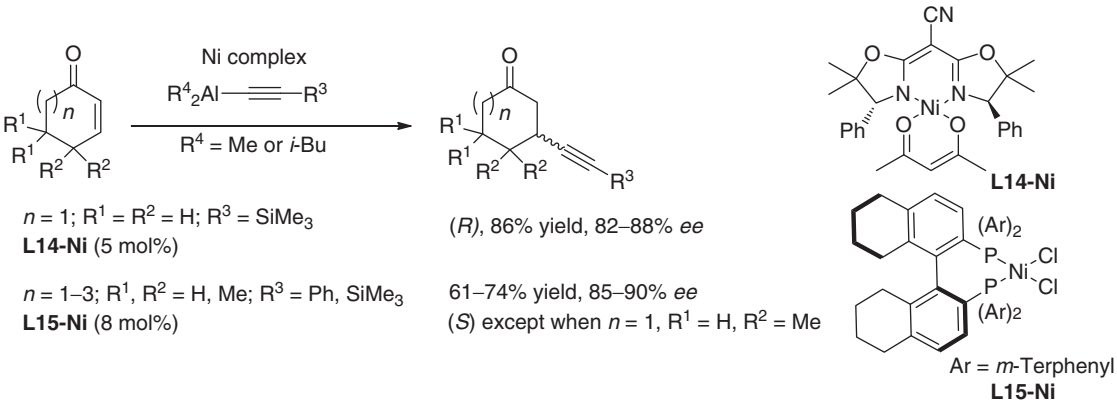
In the field of heterobimetallic catalysis, Kozlowski developed a family of BINOL-based salen-Ni(II) complexes from which **L13-Ni** showed a good *ee* (90%) in the addition of benzyl malonate on cyclohexenone (Scheme 172).[406]

Extension to other substrates was studied but poor results were observed.[407] A bifunctional catalysis was proposed where the Lewis acidic Ni(II), coordinated to the salen motif, activates the electrophile partner and the naphthoate group acts as a base toward the malonate, whereas the two reacting groups are brought closer, thanks to coordination.[407]

In 2004, Corey reported the first example of an enantioselective-catalyzed conjugate addition of an alkynyl nucleophile to a cyclic enone.[408] Using 5 mol% of bisoxazoline/Ni(II) complex **L14-Ni**, a good *ee* could be reached in the addition of dimethylaluminum TMS-acetylide on cyclohexenone, provided that the aluminum acetylide is carefully (excess of either TMSCCLi or Me_2AlCl must be avoided) prepared (Scheme 173). Later, extension to the conjugate addition of diisobutyl(phenylethynyl) aluminum to some cyclohexenones, cycloheptenone, and cyclooctenone was reported by the same group, but using 8 mol% of



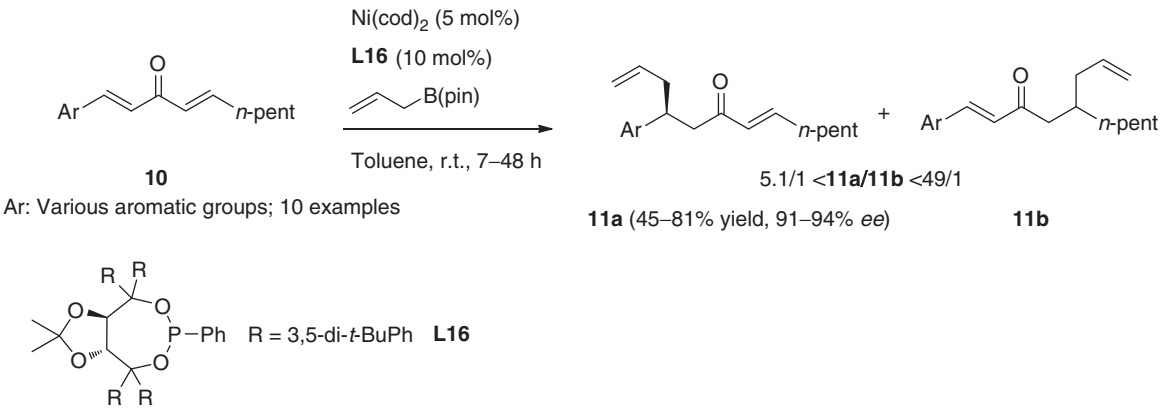
Scheme 172 Enantioselective **L13-Ni**-catalyzed conjugate addition of benzyl malonate on cyclohexenone.



Scheme 173 Enantioselective Ni-catalyzed conjugate addition of aluminum acetylides to cyclic enones.

bisphosphine/Ni(II) complex **L15-Ni** as the catalyst (Scheme 173). Enantioselectivities (up to 90%) were similar to those reached under the previously reported conditions.[409]

As the enantioselective-catalyzed conjugate addition of allyl groups has been rarely reported, the results published by Morken in 2008 are noteworthy.[410] Various arylidene alkylidene ketones **10** could be regio- and enantioselectively allylated by allylB(pin) in moderate to good yields, using $Ni(cod)_2$ as the metal source and TADDOL-based phosphonite **L16** as the chiral ligand (Scheme 174). The alkylidene fragment, which is essential for the reaction to proceed, can also be attacked but the major product arises from the addition on the arylidene fragment. It was observed that the nature of the aromatic group has an influence on the chemoselectivity and the reaction rate but not on the enantioselectivity, which was in all cases very high (up to 94%). Careful mechanistic investigations were performed and an oxidative addition-transmetallation-reductive elimination-type process was proposed for this reaction.

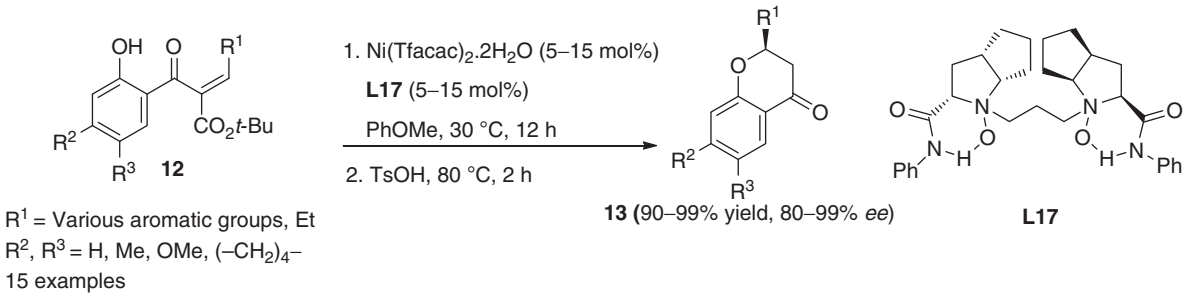


Scheme 174 Enantioselective Ni-catalyzed conjugate addition of allyl groups on enones.

Recently, the same group studied the analogous addition on alkyl-substituted enones.[368b] However, Pd-based catalysts proved to be superior to Ni catalysts for this application (see Section 4.04.4.1.1.1).

4.04.5.1.2 Addition of oxygen nucleophiles

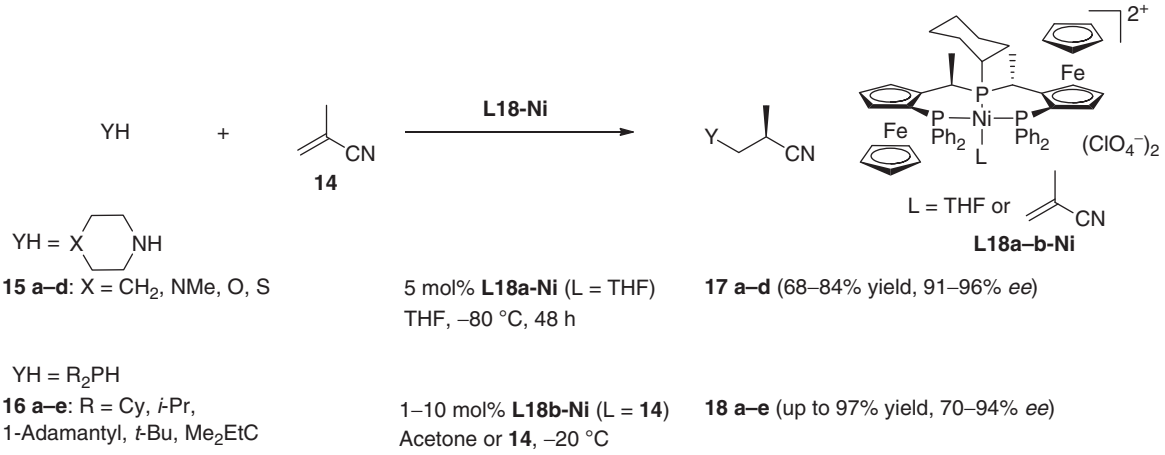
Using chiral *N,N′*-dioxide ligand **L17**, the intramolecular addition of the phenol group on activated enones within **12** led, after decarboxylation, to flavanones **13** in good to excellent *ee*s (up to 99%).[411] Interestingly, the reaction could be run in the presence of oxygen and moisture and various flavanones, which are interesting scaffolds for medicinal chemistry, could be isolated in very high yields (Scheme 175).



Scheme 175 Intramolecular addition of phenols on active enones.

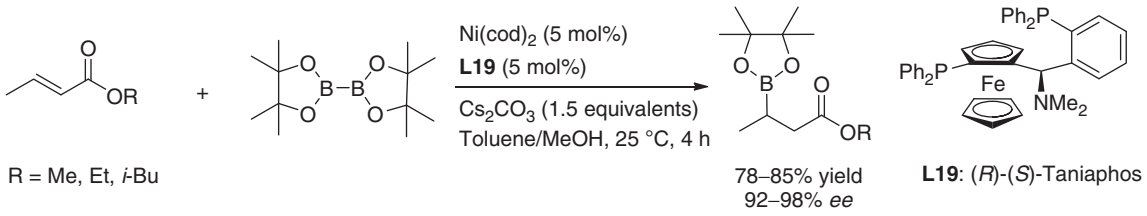
4.04.5.2 Unsaturated Esters and Nitriles

Togni explored the asymmetric addition of various amines on *α,β*-unsaturated nitriles and esters (also referred as asymmetric hydroamination of activated olefins) using Ni/triphosphine **L18-Ni** complex in both organic solvents[412] and ionic liquids.[413] Very high *ee*s (up to 96%) and good yields were observed in the addition of cyclic secondary amines on methacrylonitrile **14** when reactions were run at low temperature in THF (Scheme 176). Many other amines and activated olefins were tested but poor enantioselectivities were observed. The catalytic system was also extended to asymmetric addition of phosphines on **14** (hydrophosphination).[414] The catalytic system, which proved to give valuable results only with bulky secondary phosphines and **14**, afforded the expected products **18a–e** with high to excellent *ee*s (Scheme 176). Deep mechanistic studies were undertaken whose results agree with a mechanism where phosphine attacks the unsaturated nitrile, activated by coordination to the metal center, followed by a rate-determining protonation step. It is worth mentioning that such a mechanism is likely to occur in **L18-Ni**-catalyzed related hydroamination.



Scheme 176 **L18a–b-Ni**-catalyzed addition of amines and phosphines on methacrylonitrile.

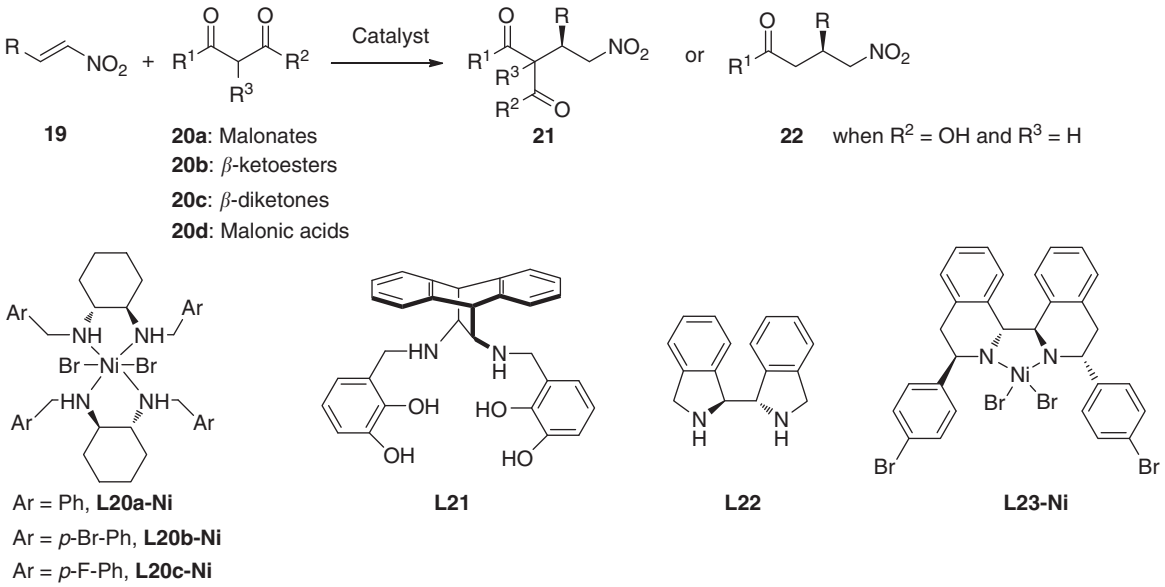
The formation of the C–B bond was also investigated with a catalytic system based on $Ni(cod)_2$ and chiral P-P and P-N ligands. Using the most efficient ligand (taniaphos **L19**), the 1,4-addition of bis(pinacolato)diboron on crotonoate esters produced *β*-boryl esters in good yields and high *ee*s (Scheme 177).[379] Little lower *ee*s were obtained using the corresponding Pd-based catalysts.



Scheme 177 Ni/Taniaphos-catalyzed addition of bis(pinacolato)diboron on crotonoate esters.

4.04.5.3 Nitroolefins

Owing probably to the high potential of the nitro group in organic synthesis, significant effort has been made to realize 1,4-conjugate addition on nitroalkenes. Among nucleophiles, malonates and related 1,3-dicarbonyl nucleophiles were the most studied and the results obtained with acyclic ones are depicted in Scheme 178 and Table 4.[415]



Scheme 178 Enantioselective Ni-catalyzed conjugate addition of β-dicarbonyl compounds on nitroalkenes.

Using complexes **L20a-Ni** and **L20b-Ni** based on readily available *trans* 1,2-diaminocyclohexane, Evans studied the enantioselective addition of various malonates, β-ketoesters and β-diketones on a wide range of nitroalkenes (entries 1–3).[415a,b] Aside from the case of alkyl-substituted nitroolefins on the one hand and β-diketones on the other, where slightly lower *ee*s were reached, the adducts were isolated in both high yields and *ee*s. In the case of β-ketoesters, similar and very good enantiocontrols were observed for both diastereoisomers. Interestingly, some experiments could be performed successfully on a 20 mmol scale at lower catalyst loading (0.1 mol%). It is worth noting that the potential of the **L20a-Ni**-catalyzed addition of β-ketoesters on nitroolefins was later illustrated in the total synthesis of (−)-stenine.[416] Besides, the catalytic system was also evaluated in the enantioselective decarboxylative Michael addition on β-ketoacids (R^2 = OH), which afforded the products in good to high *ee*s and moderate to very good yields (entry 4).[415b] The decarboxylative Michael addition on nitroolefins was also investigated starting from malonic acid half-thioesters (R^1 = SBn, R^2 = OH) and using 10 mol% of an heterobimetallic (Ni/La) complex made up of salan ligand **L21**.[415e] Interesting *ee*s (up to 94%) were observed with aromatic and heteroaromatic electrophilic partners (entry 5), whereas significantly poorest results were obtained starting from alkyl counterparts. Biisoindoline **L22** was also evaluated as ligand for the Ni-catalyzed enantioselective addition of malonates on nitroalkenes (mostly aromatic), but *ee*s were lower (72–90%) than those obtained with **L20a-Ni**.[415d] The **L23-Ni**-catalyzed addition of malonates on nitroalkenes gave noteworthy results in terms of *ee*s and yields (entry 6). However, relatively few substrates were tested and the reaction was performed at high temperature (80 °C).[415h]

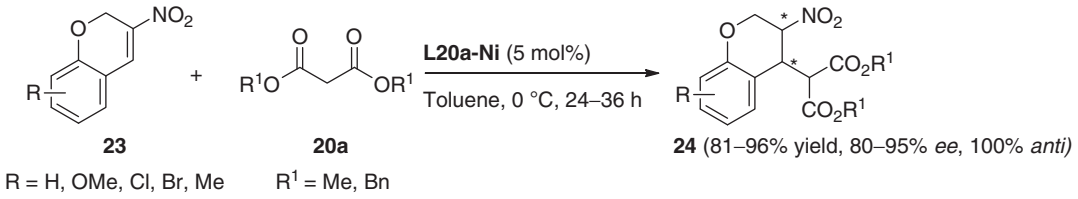
Starting from 2-bromomalonates, a tandem process involving successively an enantioselective **L20c-Ni**-catalyzed 1,4-addition on (hetero)aromatic nitroolefins and then a base-induced cyclization afforded nitrocyclopropanes in good to very high enantioselectivities (85–99%) and complete diastereoselectivities.[417]

The case of cyclic nitroalkenes was also investigated.[415f] The reaction of 3-nitro-2*H*-chromenes **23** with methyl and benzyl malonates in the presence of 5 mol% of in **L20a-Ni** provided **24** in good to high enantioselectivities and complete *anti* selectivity (Scheme 179). On the contrary, β-diketones led to racemic adducts.

Table 4 Enantioselective Ni-catalyzed conjugate addition of β-dicarbonyl-type compounds on nitroalkenes

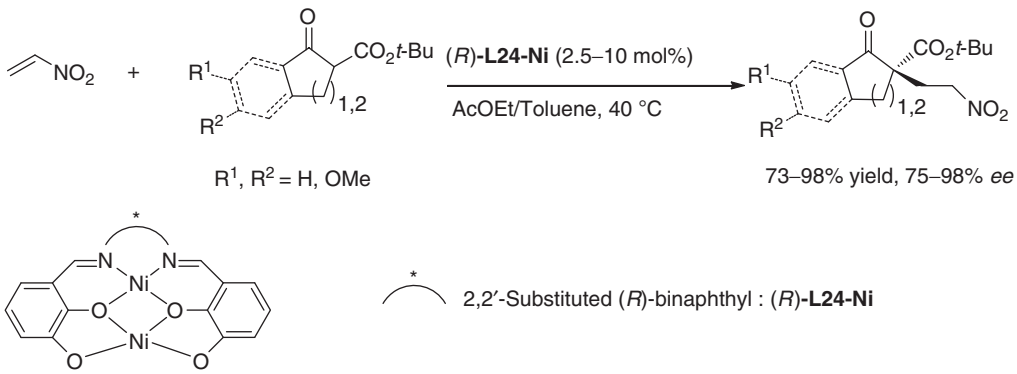
Entry	*Ligand or catalyst*	*Conditions*	*R*	*R^1, R^2*	*R^3*	*Yield (%)*	*ee (%)*	*References*
1	**L20a-Ni or L20b-Ni**	2 mol% **L20-Ni**, toluene, r.t. or 50 °C	Aryls, heteroaryl, alkenyl, alkyls	$R^1=R^2=$OMe, OEt, O*i*-Pr, O*t*-Bu, OBn	H, Me, NHAc	82–99	89–95	415a,b
2	**L20a-Ni**	2 mol% **L20a-Ni**, THF or toluene, r.t.	Ph, *p*-Br-Ph	$R^1=$Me, *i*-Pr, Ph, $R^2=$OMe, OEt, O*t*-Bu	H	94–99	85–94[a]	415a,b
3	**L20b-Ni**	2 mol% **L20-Ni**, THF or toluene, r.t.	Ph	$R^1=R^2=$Me, Et	H	88–94	88–92	415b
4	**L20b-Ni**	5 mol% **L20b-Ni**, THF, r.t.	Aryls, alkenyl, alkyl	$R^1=$Aryls, $R^2=$OH	H	50–99	77–94	415b
5	**L21**	10/10/10 mol% Ni$(OAc)_2$/La(O-*i*-Pr)$_3$/**L21**, 20 mol % DPPH[b], THF, r.t.	Aryls, heteroaryls, alkenyl	$R^1=$SBn, $R^2=$OH	H	78–99	84–94	415e
6	**L23-Ni**	2 mol% **L23-Ni**, 5 mol% NMM[c], toluene, 80 °C	Aryls, heteroaryl, alkenyl	$R^1=R^2=$OMe, OEt	H	92–99	91–99[d]	415h

[a] *dr*. 1/1–2.5/1.
[b] DPPH:1,6-bis(diphenylphosphoryl)hexane.
[c] NMM: *N*-methylmorpholine.
[d] Opposite configuration to this depicted in **Scheme 178**.



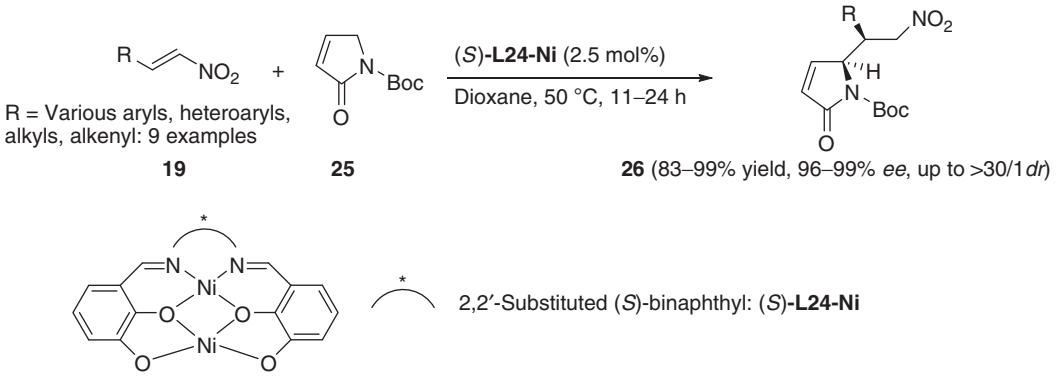
Scheme 179 Ni-catalyzed conjugate addition of malonates to cyclic nitroalkenes.

The addition of cyclic β-ketoesters was also explored using homobimetallic Ni complex (*R*)-**L24-Ni** based on a salen-type ligand (Scheme 180).[415g] In most cases, the reaction afforded the products, having a quaternary chiral center, in high *ee*s and yields. A much moderate reactivity was noticed with analogous acyclic β-ketoesters.



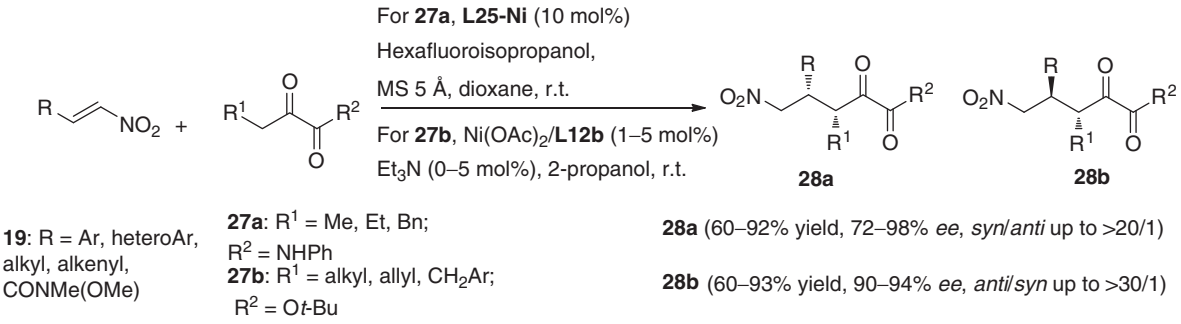
Scheme 180 **L24**-catalyzed conjugate addition of cyclic β-ketoesters to nitroethylene.

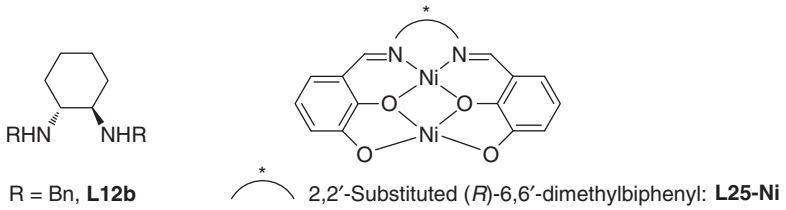
The (*S*)-enantiomer of the latter complex is an efficient catalyst for the conjugate addition of α,β-unsaturated γ-butyrolactame **25** on nitroalkenes, as vinylogous adducts were isolated in excellent yields, *ee*s (96–99%) and *dr* irrespective of the class of nitroalkene employed (Scheme 181).[418]



Scheme 181 **L24-Ni**-catalyzed conjugate addition of γ-butyrolactame to nitroalkenes.

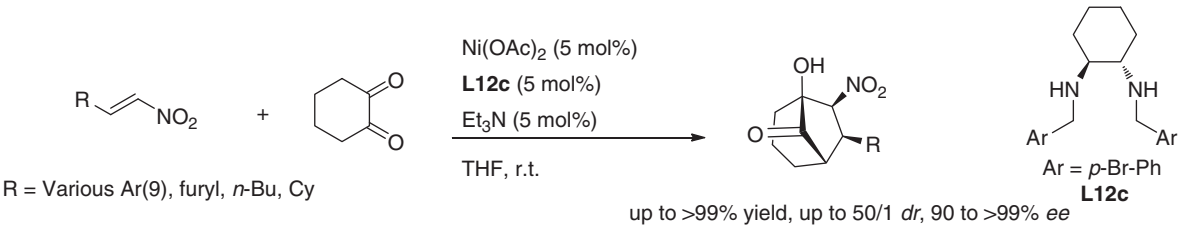
α-Dicarbonyl compounds were also tested as nucleophilic partners. The 1,4-addition of α-keto anilides **27a**[419] and α-ketoesters **27b**[420] on different classes of nitroalkenes were independently explored, using respectively **L25-Ni** and Ni/**L12b** as catalytic systems (Scheme 182). In both studies, the products were isolated in good to high *ee*s, but the *syn*/*anti* selectivities were opposite.





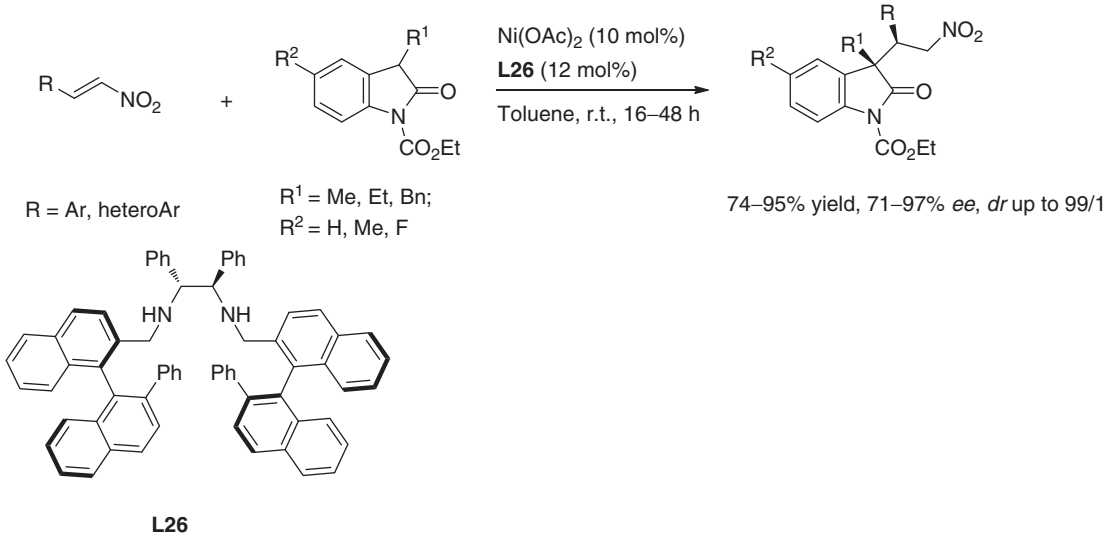
Scheme 182 Enantioselective Ni-catalyzed 1,4-addition of α-ketoesters and α-ketoanilides.

A tandem process involving a Michael addition of α-diketones on nitroalkenes and then a Henry reaction using Ni/**L12c** as catalyst was described in 2012.[421] The reaction was particularly exemplified with 1,2-cyclohexanedione which was added on nitroolefins having various types of substituents in the β-position (Scheme 183). In most cases, the bicyclic products were obtained in good to excellent yields, high diastereoisomeric ratios, and *ee*s (resp. up to 50/1 and up to >99%). Few experiments were run with other α-diketones. Although acyclic ones proved to be valuable substrates giving monocyclic products in high *ee*s (90–97%), the *ee* was diminished with 1,2-cyclopentanedione (51%).



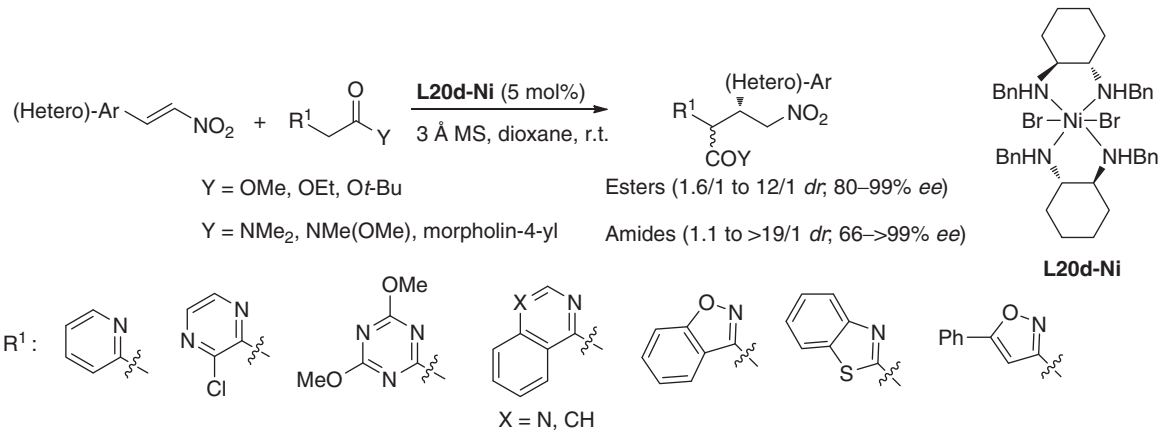
Scheme 183 Enantioselective tandem Michael/Henry process starting from α-diketones and nitroalkenes.

Among the papers reporting the use of 3-substituted oxindoles as nucleophilic partners,[415g,422] the most valuable results were obtained using the 1,2-diamine **L26** as chiral ligand.[422b] Good to high *ee*s (up to 97%) and *dr* were reached with a broad range of aromatic nitroalkenes (Scheme 184). On the contrary, no reaction occurred when oxindoles were not protected as carbamates or if the reaction was run with aliphatic nitroolefins.



Scheme 184 Enantioselective Ni/**L26**-catalyzed addition of 3-substituted oxindoles to nitroalkenes.

The addition of various azaaryl-acetates and -acetamides on (hetero)aryl-nitroalkenes was explored using Evans' complex **L20d-Ni** as catalyst (Scheme 185). With the former substrates, the products, which were in most cases subject to epimerization, were formed in moderate to good diastereoselectivities and good to high *ee*s (80–99%). When acetamide counterparts were reacted, higher diastereoisomeric ratios could be reached in some cases, but *ee*s were in the same range. It was noted that aliphatic nitroalkenes were not efficient substrates in the conditions used.[423]



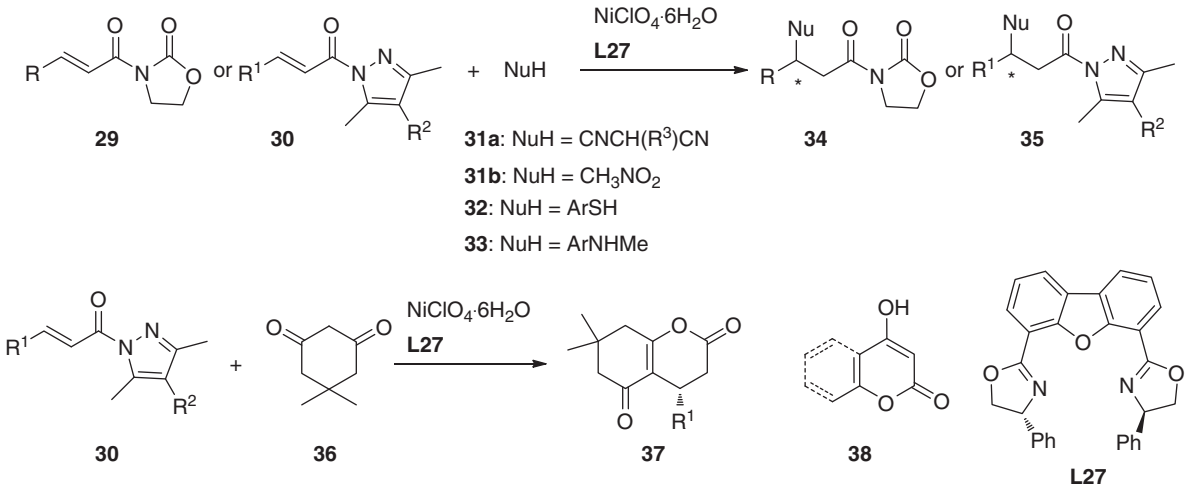
Scheme 185 Enantioselective **L20d-Ni**-catalyzed conjugate addition of azaaryl-acetates and -acetamides on nitroalkenes.

4.04.5.4 α,β-Unsaturated Imides and Amides

4.04.5.4.1 Addition of C-nucleophiles

The enantioselective 1,4-conjugate addition on 3-(2-alkenoyl)-2-oxazolidinones and 1-(2-alkenoyl)-3,5-dimethylpyrazoles was explored with many nucleophiles using a $Ni(ClO_4)_2{\cdot}6H_2O$/**L27**-based catalytic system (Scheme 186). Dealing with C-nucleophiles, good *ee*s could be reached in the addition of malononitrile to some alkenoyl oxazolidinones using 10 mol% of two catalysts, the Lewis acid chiral Ni complex and an amine (Table 5, entry 1).[424] Under similar conditions, good enantioselectivities were also observed using various 1-(2-alkenoyl)-3,5-dimethylpyrazoles as substrates (entry 3). When the reaction was

run in the absence of the amine but in an alcoholic solvent, the combination of $Ni(ClO_4)_2{\cdot}6H_2O$ and **L27** could be extended very successfully to substituted malononitriles (entry 4).[425] Products having two quaternary carbons could also be obtained starting from *β*,*β*-disubstituted alkenes, but enantioselectivities were less impressive (up to 76%).[425] Kanemasa also explored the addition of nitromethane on a broad range of 1-(2-alkenoyl)-3,5-dimethylpyrazoles under similar conditions and obtained the products in varying yields, but in many cases in excellent *ee*s (up to 98%, entry 2).[426] When dimedones were used as nucleophile precursors, bicyclic products arising from a sequential process involving Michael addition followed by elimination of the pyrazole group were obtained in high *ee*s (Scheme 186 and Table 5, entry 5).[425,427] The application of the process to the addition of analogous nucleophiles, such as **38** (see Scheme 186), to various 1-(2-alkenoyl)-3,5-dimethylpyrazoles gave the expected polycyclic products in good to very high *ee*s. Few examples of the reactions of pyrazole acceptors were reinvestigated using, in alcoholic solvent, $Ni(OAc)_2{\cdot}4H_2O$ instead of $Ni(ClO_4)_2{\cdot}6H_2O$ as the metal source.[428] This led to slightly better *ee*s with nitromethane (98%) and malononitrile (92%), whereas the addition of dimedone could be run with diminished catalyst loading (0.5 mol%).



Scheme 186 Ni/**L27**-catalyzed conjugate additions to 3-(2-alkenoyl)-2-oxazolidinones and 1-(2-alkenoyl)-3,5-dimethylpyrazoles.

Table 5 Ni/**L27**-catalyzed conjugate additions to 3-(2-alkenoyl)-2-oxazolidinones and 1-(2-alkenoyl)-3,5-dimethylpyrazoles

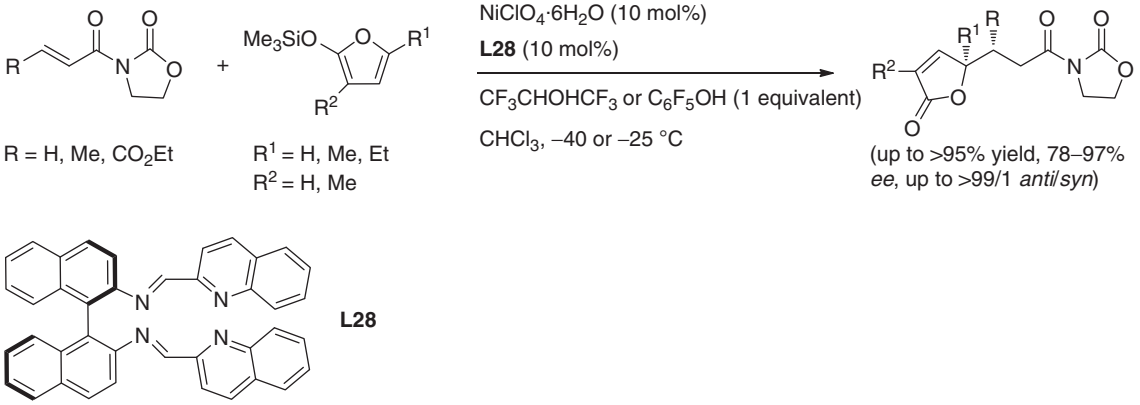
Entry	*Ni/Ligand (mol%)*	*Substrate*	*NuH*	*Conditions*	*Yield (%)*	*ee (%)*	*References*
1	10/10	**29**, R = Me, *n*-Pr, *i*-Pr, *t*-Bu, Ph	**31a** (R^3 = H)	TMP (10 mol%), CH_2Cl_2, −20 °C or r.t.	38–100	75–94	424
2	10/10	**30**, R^1 = alkyl, alkenyl, ester, (hetero)Ar, R^2 = H	**31b**	TMP (10 mol%), $MeNO_2$/THF (1/1), −20 °C, 0 °C or r.t.	39–96	77–98	426
3	10/10	**30**, R^1 = alkyl, Ar; R^2 = Br	**31a** (R^3 = H)	TMP (10 mol%), Ac_2O (10 mol%), THF, r.t.	82–94	78–93	424
4	10/10	**30**, R^1 = Me, *i*-Pr, Ph, CO_2Et, R^2 = H	**31a** (R^3 = Me, Bn)	*t*-BuOH/THF, r.t.	33–92	91–99	425
5	10/10	**30**, R^1 = alkyl, alkenyl, (hetero)Ar; R^2 = Br	**36**	TMP (10 mol%), Ac_2O (2 equivalents), THF, r.t.	53–99	89–99	427

Notes: TMP: 2,2,6,6-Tetramethylpiperidine.

Besides, the Ni-catalyzed conjugate addition of 2-silyloxyfurans on 3-(2-alkenoyl)-2-oxazolidinones was studied using Quinolyl–Schiff base ligand **L28** (Scheme 187). Four nucleophilic precursors and three acceptors were used, and the adducts were isolated in high yields, good to very high *ee*s, and almost complete *anti*-selectivity.[429]

4.04.5.4.2 Addition of sulfur and nitrogen-nucleophiles

The $Ni(ClO_4)_2{\cdot}6H_2O$/**L27** catalytic system was also evaluated in the conjugate addition of *S*- and *N*-nucleophiles to alkenoyl oxazolidinones (Scheme 186). The addition of a series of arylthiols on 3-crotonoyl-2-oxazolidinone afforded the adducts in most cases in good yields and good to high *ee*s (Table 6, entry 1).[430] The outcome of the addition of secondary arylamines appeared nucleophile-dependent (entry 2).[431]



Scheme 187 Ni/**L28**-catalyzed conjugate addition of 2-silyloxyfurans.

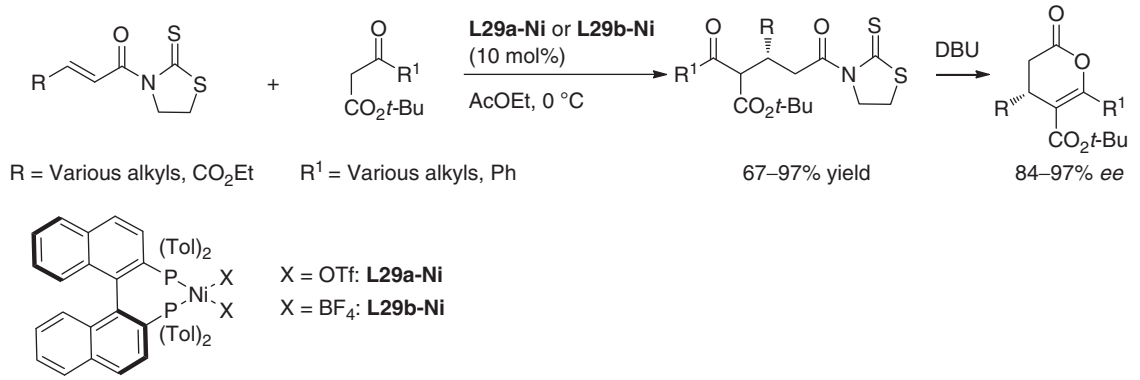
Table 6 Ni/**L27**-catalyzed addition of *S*- and *N*-nucleophiles on alkenoyl oxazolidinones

Entry	*Ni/Ligand (mol%)*	*Substrate*	*NuH*	*Conditions*	*Yield (%)*	*ee (%)*	*References*
1	10/10	**29**, R = Me	**32**	THF, r.t. or TMDN (10 mol%), CH_2Cl_2/THF, 0 °C	30–100	78–97	430
2	5/5	**29**, R = Me, Pr	**33**	CH_2Cl_2, r.t.	23–87	48–96	431

Notes: TMDN: *N,N,N′,N′*-Tetramethyl-1,8-diaminonaphthalene.

4.04.5.5 Miscellaneous Michael Acceptors (Unsaturated *N*-Acylthiazolidinethiones, bis-Phosphonates, and α-Ketoesters)

Evans reported a highly enantioselective Ni/Tol-BINAP (**L29a-Ni** or **L29b-Ni**)-catalyzed addition of various β-ketoesters on a series of *N*-acylthiazolidinethiones (Scheme 188).[432] The adducts were efficiently transformed into functionalized dihydropyrones.



Scheme 188 Enantioselective Ni-catalyzed conjugate addition of β-ketoesters to *N*-acylthiazolidinethiones.

The Ni-catalyzed addition of substituted β-nitroesters on unsaturated gem-bisphosphonates was investigated using (*R*)-**L24** (see Scheme 180) as chiral ligand. The products, which belong to a class of molecules having pharmacological applications, were in all cases with the exception of one, isolated in only fairly good *ee*s (76–93%).[433] A number of substituted unsaturated α-ketoesters were also explored as Michael acceptors for 4-hydroxycoumarin, using a Ni/*N,N′*-dioxide-based catalyst. The products were obtained in excellent yields, whereas *ee*s were at most 90%.[434]

4.04.5.6 Extended Michael Acceptors

Extended (dienic) systems were sometimes tested as substrates in the works presented in the previous sections. In all cases, the formation of 1,6-adducts was not mentioned and only 1,4-adducts were isolated.

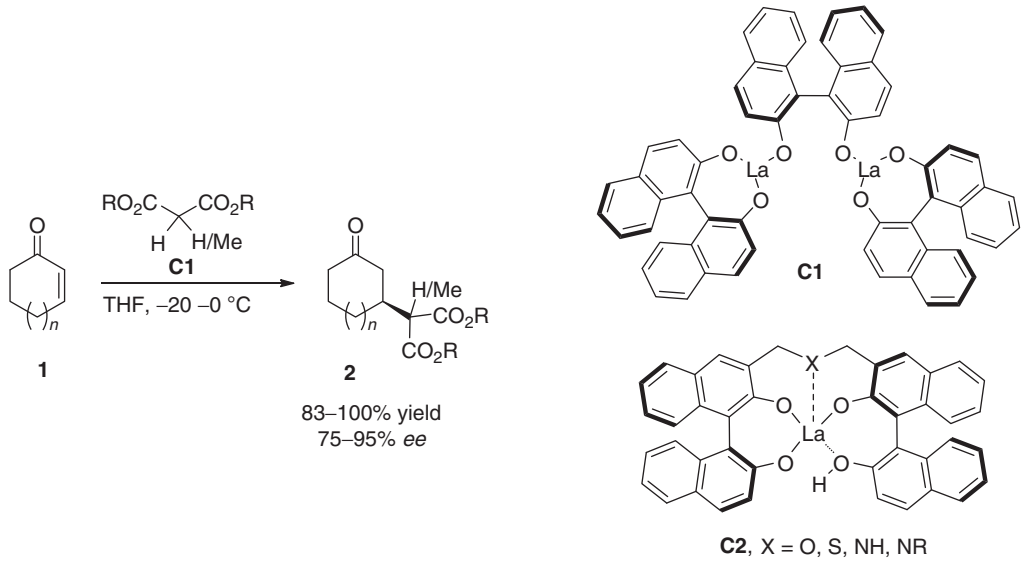
4.04.6 Rare Earth Element-Catalyzed Enantioselective Conjugate Addition

The 1980s and the 1990s have witnessed a growing interest for new organic transformations mediated by rare earth metal reagents. Considerable work has been reported and lanthanides, scandium, and yttrium are still studied, leading to the development of valuable reactions. Rare earth elements have been used in polymerization, reduction processes, oxidation, coupling reactions and as Lewis acids in addition reactions: aldol, nitrolaldol, or Michael additions. Herein, the authors provide a comprehensive overview of the utilization of rare earth metals associated with chiral ligands to promote enantioselective additions to electron-deficient olefins. The different classes of Michael acceptors will be reviewed (cyclic and acyclic enones, α,β-unsaturated esters, ketoesters or thioesters, nitrololefins, α,β-unsaturated amides and aldehydes, etc.) as well as the various nucleophiles that have been employed (malonates and others C-nucleophiles, alcohols, thioalcohols, amines, etc.). Examples of conjugate cyanations, cyclopropanations, and epoxidations will be also presented.

4.04.6.1 α,β-Unsaturated Enones

4.04.6.1.1 Addition of C-nucleophiles

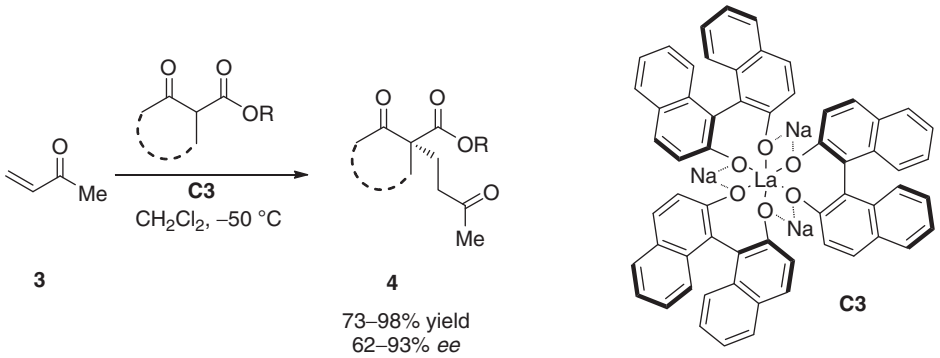
The group of Shibasaki was very active in the use of rare earth metal alkoxides (lanthanum or yttrium) as a base in addition reactions. For instance, several asymmetric BINOL-rare earth metal–lithium bimetallic complexes[435] have been developed and found effective in enantioselective nitroaldol reactions.[436] However, the same catalytic system using lanthanum exhibited low activity in Michael addition of malonate derivatives to cyclic enones (poor yields and low enantioselectivities). It was observed that without lithium both high yields and asymmetric induction could be reached.[437a] As depicted in Scheme 189, BINOL–lanthanum complex **C1**, generated from La(O*i*-Pr)$_3$ and BINOL, various malonate derivatives were added to cyclopentone and cyclohexenone to give adducts **2** in almost quantitative yields and enantioselective excesses up to 95%. Unfortunately, this system was less competent for acyclic enones. Using other alkali metals than lithium, sodium for instance (complex **C3**), showed a beneficial effect in speeding up the reaction duration, thanks to the basic and Lewis acid properties of the heterobimetallic lanthanum–sodium–BINOL complex.[437b] Of note, other lanthanides such as praseodymium or gadolinium led to worse results for asymmetric induction.



Scheme 189 Lanthanum–BINOL complex-catalyzed enantioselective Michael addition.

The catalytic system was further improved by the modulation of BINOL moiety. The linkage of two BINOL units by a bridge containing a heteroatom led to the formation of new lanthanum complexes **C2** which led to better catalytic activities with enantioselectivity improvement, especially for amino-derived bridges.[438] Moreover, complexes exhibited a better stability allowing their easy isolation and recycling (up to five cycles). The *ee*s obtained for malonate addition to a variety of cyclic enones were high but moderate for acyclic substrates.

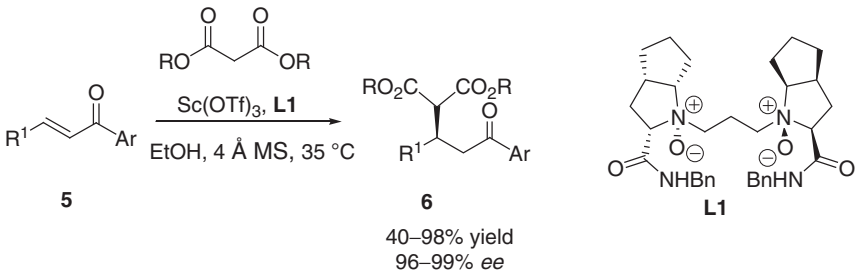
The issue of acyclic enones was addressed by Shibasaki and coworkers using the heterobimetallic lanthanum–sodium–BINOL complex **C3** (Scheme 190).[439] A solvent screening showed a strong influence on the stereocontrol; toluene and dichloromethane led to highest enantiomeric excesses. Thus, several adducts **4** of the MVK **3** were isolated with moderate to good enantiopurities. Similar results were obtained with acrylates as Michael acceptors. Later, a heterogenization of lanthanum with fluoroapatite as macroligand and tartaric acid as chiral ligand was attempted and led to the formation of the adduct with moderate *ee*s (up 60%).[440]



Scheme 190 Lanthanum-sodium-BINOL complex-catalyzed enantioselective Michael addition to methylvinylketone **3**.

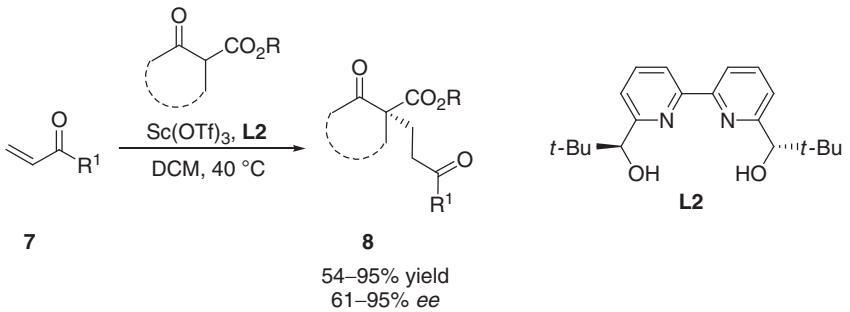
In addition to lanthanum, other rare earth metals were described to catalyze the enantioselective Michael addition of 1,3-dicarbonyl compounds to enones. For instance, early nineties, Scettri reported that europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate ($Eu(tfc)_3$] mediated the conjugate addition of 1,3-ketoesters to MVK with up to 36% *ee*.[441]

Nakajima demonstrated the potential of chiral *N,N′*-dioxide-scandium triflate to serve as catalyst for asymmetric Michael addition of *β*-ketoester to **3** (up to 84% *ee*) or the acrolein (up to 75% *ee*).[442] Recently, Feng improved these results using structurally advanced *N,N′*-dioxide **L1** derived from L-ramipril acid as chiral ligand (Scheme 191).[443] A series of ketoester adducts were obtained with high yields and excellent enantioselectivities. Other rare earth metals, such as yttrium(III) triflate or lanthanum (III) triflate, were tested; however, no chiral induction was observed.



Scheme 191 Asymmetric Michael addition promoted by chiral *N,N′*-dioxide complex.

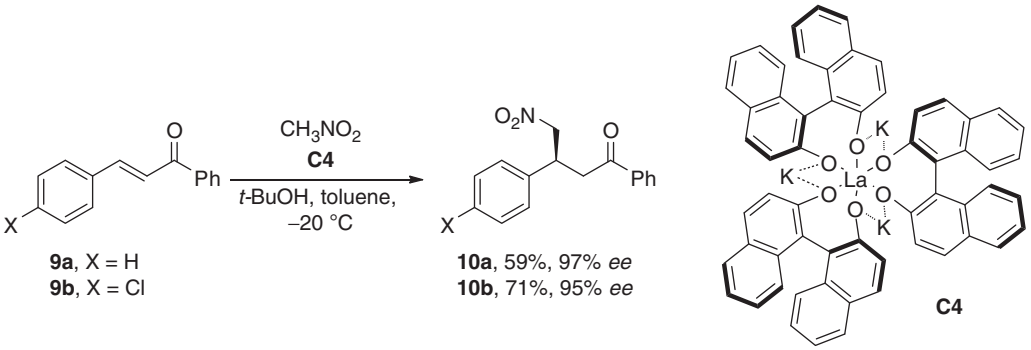
Other ligands associated with a scandium salt were tested in Michael additions; Kobayashi surveyed chiral bis-pyridine-based alcohols.[444] Ligand **L2** and scandium(III) triflate proved to catalyze smoothly Michael addition in dichloromethane (DCM) to afford the corresponding adducts **6** with both good chemical yields and excellent stereocontrols in most of the examples (Scheme 192). However, this reaction has been exemplified to mostly aromatic ketones. Importantly, reactions need to be carried out at low concentrations to get high enantioselectivities. Kumagai and Shibasaki investigated an analog reaction with *α*-cyanoketones as nucleophiles and an amide-based ligand.[445] Several rare earth metals were screened and no or low *ee* values were obtained for Sc, La, Pr, Sm, Gd, Er, and Yb. Only yttrium salt afforded a good chiral induction which was further improved up to 99% *ee* during the optimization process. The inspection of several *α*-cyanoketones and acyclic *α,β*-unsaturated ketones revealed a good reaction scope.



Scheme 192 Scandium-catalyzed enantioselective Michael addition.

Lindström and Wennerberg focused their research on the development of an asymmetric Lewis acid for Michael addition, which will be water compatible.[446] The combination of an ytterbium salt, $Yb(OTf)_3$, with α-amino acids was found able to promote the aqueous biphasic Michael addition of 1,3-diketones to cyclic enones with *ee* up to 79%. Regrettably, scope investigation showed that other Michael acceptors gave poor or no chiral induction.

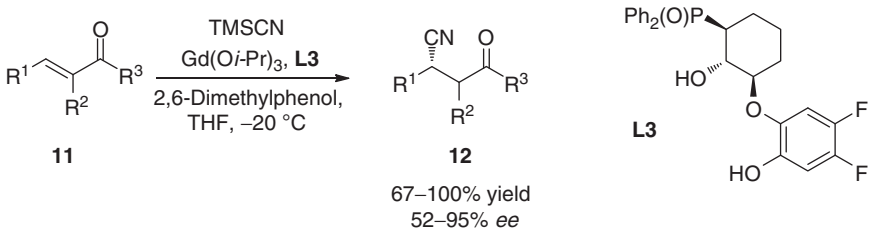
Besides the benchmark malonates and other 1,3-dicarbonyl compounds, other C-nucleophiles can be added to enones in an enantioselective manner using rare earth elements. For instance, the multifunctional catalyst LaK_3tris-binaphthoxide **C4** was tested for the addition of nitromethane to chalcones **9** (Scheme 193).[447] In the presence of *tert*-butanol, for which the role remains unclear, ketones **10** were isolated with excellent chiral purity. This addition of nitromethane to chalcones could be also performed with an excellent enatioselectivity using the scandium triflate associated with a chiral *N*,*N*′-dioxide ligand alike **L1**.[448]



Scheme 193 Lanthanum–potassium–BINOL complex-catalyzed enantioselective Michael addition of nitromethane to α,β-unsaturated ketones.

Chiral *N*,*N*′-dioxide ligands were also used with yttrium(III) triflate to promote Friedel–Crafts alkylation of β-chloro(trifluoro) methyl aryl ketones with indoles.[449] Scandium salts could be also used, whereas lanthanum and samarium analogs were found inactive. Overall, excellent results were obtained: up to 96% *ee* and 99% yield. This is one of the rare examples of Friedel–Crafts alkylation of enones catalyzed by rare earth metals. However, other Michael acceptors such as α,β-unsaturated esters were more studied.

The conjugate addition of cyanide to α,β-unsaturated ketones and more generally Michael acceptors is a valuable organic transformation, but challenging because of the two possible reaction pathways 1,2-addition and 1,4-addition. Kanai and Shibasaki developed a gadolinium-based catalytic system to perform selectively the conjugate addition with a high enantioselectivity (Scheme 194).[450] The ligand **L3**, a phosphine oxide derived from D-glucose, was found to play a key role because it directs the reactivity toward formation of 1,4-adduct **12** and also allows an excellent stereocontrol. The cyanide source (TMSCN) and a protic additive (2,6-dimethylphenol) are as well key parameters to obtained acyclic β-cyano ketones with a high optical purity (87–95% *ee*). The *ee* values for cyclic enone substrates were lower 81% *ee* for cyclohexenone and cyclootenone, 52% *ee* for cycloheptenone.

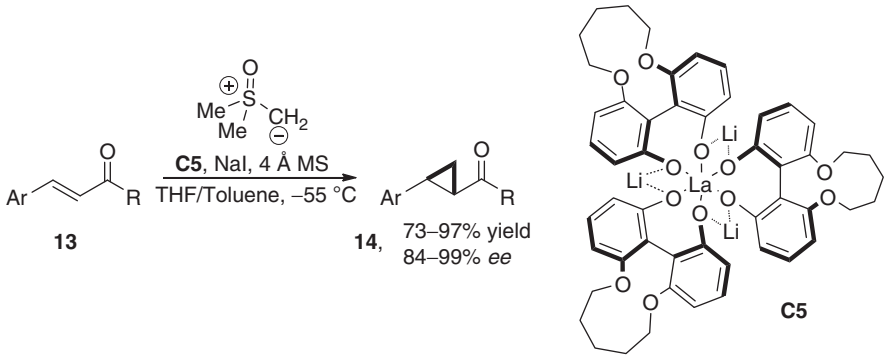


Scheme 194 Gadolinium-promoted ACA of cyanide to α,β-unsaturated ketones.

To get a new, efficient, and alternative synthetic route to enantioselective cyclopropanes, Matsunaga and Shibasaki investigated the catalytic addition of a particular C-reagent, a sulfonium ylide, onto α,β-unsaturated ketones.[451] After the optimization of reaction conditions, the catalytic system depicted in Scheme 195 afforded the preparation of cyclopropanes **14** with an excellent optical purity. Surprisingly, the BINOL analog to the lanthanum–lithium complex **C5** yielded only a racemic cyclopropane. The presence of NaI was required even if its role remains unclear. Although chalcone derivatives allowed to reach excellent *ee* values (91–99% *ee*), aliphatic ketone led to lower stereocontrol (84% *ee*).

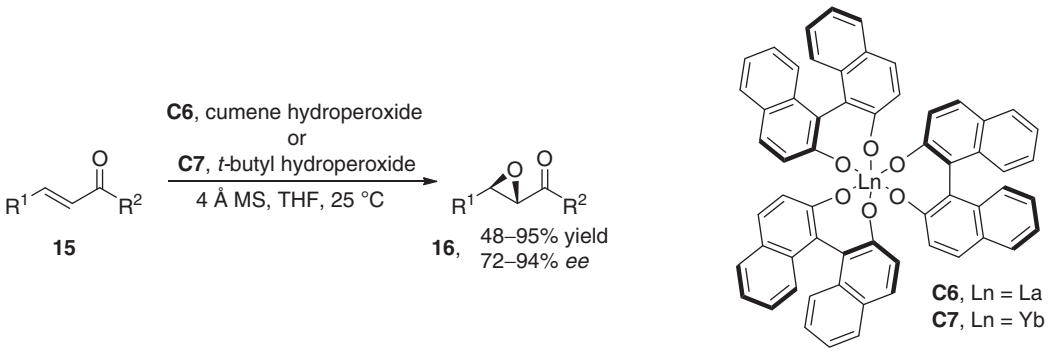
4.04.6.1.2 Epoxidation

In the history of asymmetric catalysis, epoxidation holds a respected place, notably because of the work of Sharpless, and therefore was a subject of intensive researches. Nevertheless, for a long time, electro-deficient alkenes were a recalcitrant class of substrates.



Scheme 195 Asymmetric cyclopropanation of enone mediated by a lanthanum–lithium–biphenyldiolate complex.

Because, several chiral catalytic systems were described including organocatalysts and lanthanoid-based complexes. Shibasaki and coworkers developed an efficient catalytic asymmetric epoxidation of enones using lanthanide complexes.[452] As illustrated in Scheme 196, either the lanthanum–BINOL complex **C6** or its counterpart with ytterbium **C7** was able to afford α-keto epoxides **16** with excellent enantiopurity. However, differences between the two systems were observed. **C6** performed better with cumene hydroperoxide, whereas **C7** yielded higher *ee* values with *tert*-butylhydroperoxide and was particularly efficient for the preparation of *cis*-epoxyketones.[452b] These results were further improved by the addition of additives. Surprisingly, the ytterbium-based system **C7** afforded better activities and enantioselecivities in the presence of both water and molecular sieves.[452c] The desiccant was found necessary for complex formation and water for the reaction itself. The performance of the lanthanum complex **C6** was enhanced by the addition of triphenylphosphine oxide or even better triphenylarsine oxide which triggered the formation of a new complex that was most active and effective (up to 99% yield and 99% *ee*).[452d,e] Inanaga reported a similar catalytic system containing lanthanum and BINOL with *tert*-butyl hydroperoxide as oxidative agent and phosphine oxide as additive.[453] The lanthanum–BINOL complex was successfully heterogenized by Ding through a multitopic ligand strategy.[454]



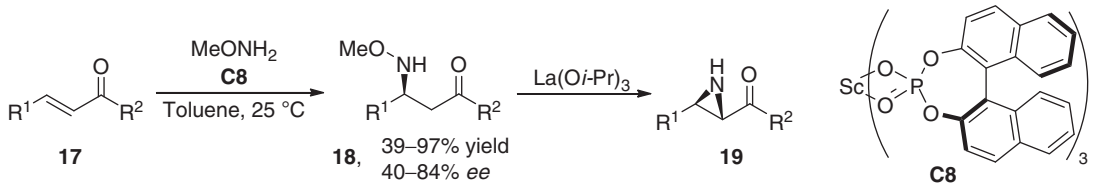
Scheme 196 Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by lanthanide complexes.

Recently, it has been reported that a chiral *N,N′*-dioxide-scandium triflate catalyst displayed good performances for the asymmetric epoxidation of enones and α,β-unsaturated amides using advantageously hydrogen peroxide.[455] Moreover, the system was tolerant of air and moisture conditions.

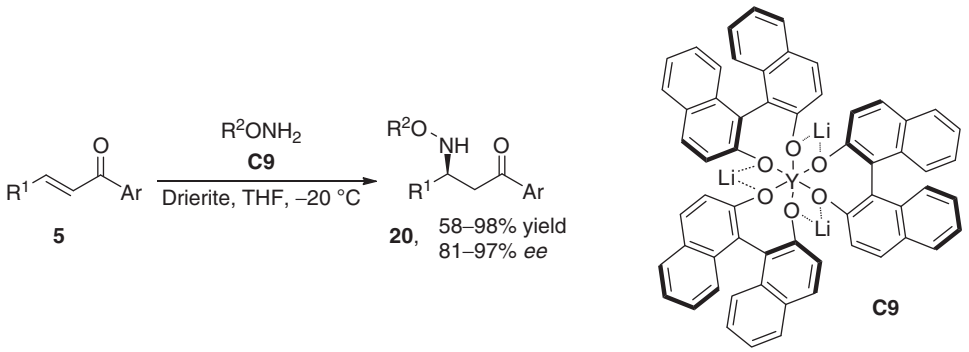
4.04.6.1.3 Aza-Michael addition

The ECA of amines to α,β-unsaturated carbonyl derivatives, the so-called aza-Michael addition, represents a straightforward and useful strategy for the preparation of optically active synthons. As an extension of his work on the synthesis of enantiopur α-keto epoxides,[453] Inanaga studied the asymmetric addition of *O*-methylhydroxylamine to acyclic enones.[456] The scandium catalyst **C8** bearing binaphtyl phosphate ligands showed a good competence to the formation of β-methoxyamino ketones **18** with modest to good chemical and optical yields (Scheme 197). A lanthanum salt achieved to ring closure reaction to form α-keto azeridines **19**. Interestingly, the authors investigated also a kinetic resolution of racemic β-methoxyamino ketones **18** using La(O*i*-Pr)$_3$ and (*R*)- or (*S*)-BINOL to get enantiomerically enriched azeridines **19**.

The series of rare-earth-alkali-metal heterobimetallic complexes developed by Shibasaki since the early 1990s were screened to carry out the enantioselective 1,4-conjugate addition of *O*-alkylhydroxylamine to enones.[457] High *ee* and yield were achieved using the YLi$_3$tris(binaphthoxide) **C9** with a low catalyst loading (down to 0.5 mol%) and a desiccant, Drierite (Scheme 198). Mechanistic studies highlighted a cooperation between the two Lewid acids of the heterobimetallic complex.[457b,c]

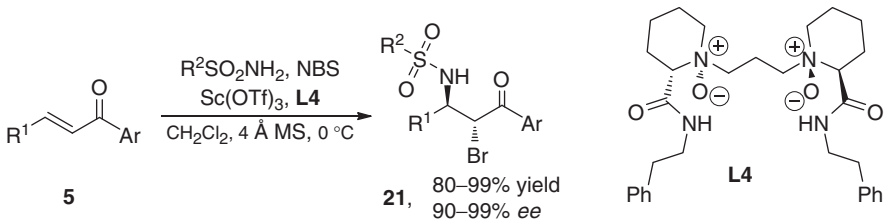


Scheme 197 Scandium-catalyzed asymmetric aza-Michael addition.



Scheme 198 Yttrium-catalyzed asymmetric aza-Michael addition.

Feng and coworkers investigated as well the enantioselective aza-Michael addition; however, they focused on other *N*-nucleophiles than *O*-alkylhydroxylamine. The chiral *N*,*N*′-dioxide-scandium triflate system previously studied[443] also showed a good ability to promote the addition of hydrazide[458a] or 1*H*-benzotriazole[458b] to *α*,*β*-unsaturated ketones. The catalytic system was also applied to a bromoamination of acyclic *α*,*β*-unsaturated aromatic ketones **5** to afford *α*-bromo-*β*-amino ketones **21** (Scheme 199).[459] When **5** was treated with sulfonimide and *N*-bromo-succinimide (NBS) in the presence of scandium triflate and chiral *N*,*N*′-dioxide ligand **L4** under mild conditions, compounds **21** were isolated as a single regio- and diastereomer with excellent optical purity. On the basis of preliminary studies, the authors proposed that the reaction mechanism proceeds via an unusual bromonium intermediate.

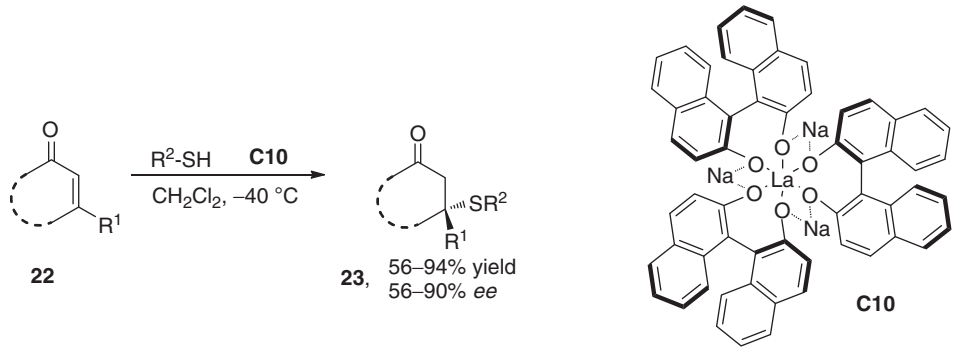


Scheme 199 Scandium-promoted asymmetric bromoamination of chalcones.

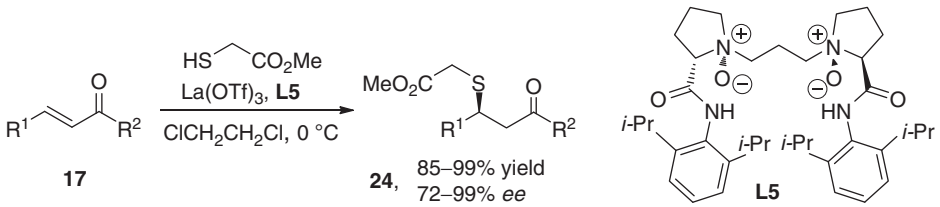
4.04.6.1.4 Sulfa-Michael addition

Having developed efficient heterobimetallic asymmetric complexes for enantioselective Michael additions using malonate derivatives, Shibasaki and coworkers scrutinized other nucleophiles. $LaNa_3$tris(binaphthoxide) **C10** was found reliable to perform the addition of various thiols to cyclic enones in an asymmetric manner (Scheme 200).[460] Only cyclopentone gave a moderate enantioselectivity (56% *ee*) and the substitution of the substrate C–C double bond led to decreased isolated yield. In 2002, Sundararajan reinvestigated Shibasaki catalyst system by replacing the BINOL by another diol, the C_2-symmetric (*R*,*R*)-(+)-2-[benzyl-(2-hydroxy-2-phenyl-ethyl)amino]-1-phenylethanol.[461] The new lanthanum complex showed a good activity for various Michael additions and was fully investigated for thiol nucleophiles.

Feng and coworkers evaluated the potential of their chiral *N*,*N*′-dioxide ligands in the sulfa-Michael addition of thioglycolate to acyclic enones.[462] The study of various rare earth triflate salts revealed a slight better activity and enantioselectivity of lanthanum over ytterbium, yttrium, indium, and scandium. A ligand screening allowed identifying **L5** with bulky *N*-substituents leading to an excellent stereocontrol (Scheme 201). Under the optimized conditions, an impressive range of optically active *β*-thio ketones **24** was synthesized with *ee* values mostly superior to 90%.



Scheme 200 Asymmetric sulfa-Michael addition using lanthanum–sodium–BINOL complexes.



Scheme 201 Enantioselective 1,4-addition of thioglycolate to chalcones mediated by lanthanum.

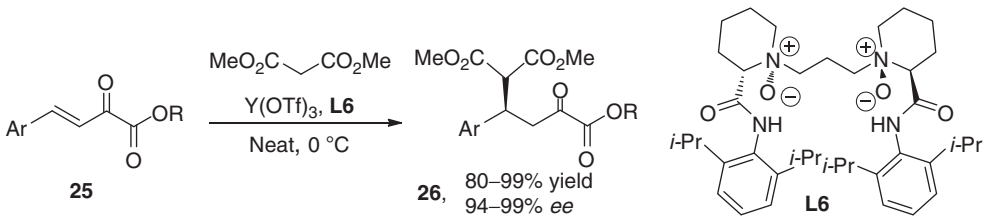
In 2011, Vaccaro[463] and Kobayashi[464] reported independently the same catalytic system efficient for the enantioselective sulfa-Michael additions to α,β-unsaturated ketones in water. The combination of scandium(III) triflate and ligand **L2** gave 1,4-thio-adducts in high yields and excellent enantioselectivities for acyclic enones.

4.04.6.2 α,β-Unsaturated Esters and Derivatives

In addition to α,β-unsaturated ketones, other substrates with an electro-deficient C–C double bond have been investigated to perform rare earth metal-catalyzed enantioselective addition: for instance, asymmetric Michael addition or Friedel–Crafts alkylation to α,β-unsaturated (thio)esters or β,γ-unsaturated α-ketoesters. To the best of our knowledge, α,β-unsaturated lactones have not been investigated so far.

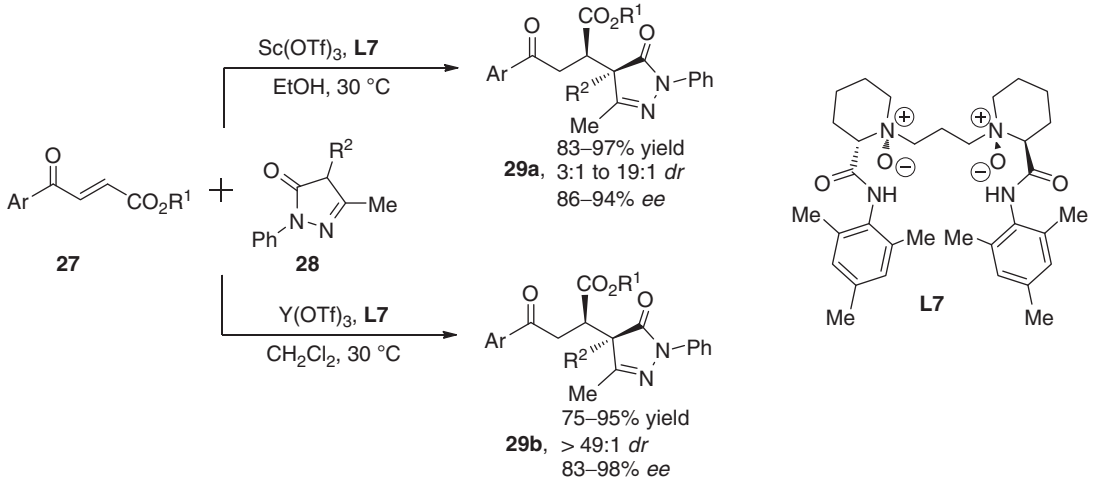
4.04.6.2.1 Addition of C-nucleophiles

In 2010, Liu and Feng reported the Michael addition of malonates to α,β-unsaturated α-ketoesters **25** using the chiral *N,N′*-dioxide ligand **L6** (Scheme 202).[465] Preliminary studies on rare earth elements showed that $Yb(OTf)_3$ or $Y(OTf)_3$ performed better than $Sm(OTf)_3$ or $La(OTf)_3$, whereas no reaction occurred with $Sc(OTf)_3$. With the optimized reaction conditions, various adducts **26** were obtained with high chemical and optical yields, using low catalyst loadings (down to 1 mol%). Moreover, these reactions were carried out without any solvents and on multigram scale.



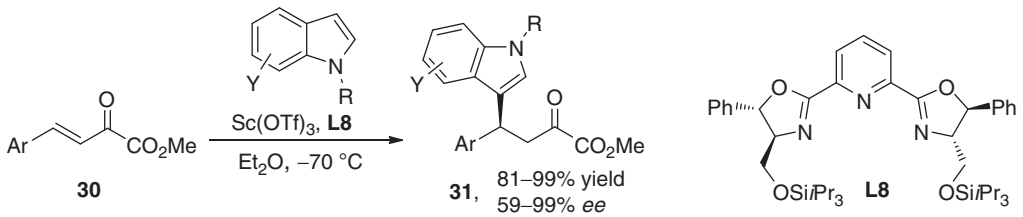
Scheme 202 Yttrium-catalyzed asymmetric Michael addition to β,γ-unsaturated α-ketoesters.

However, scandium(III) salts were found particularly competent for Michael additions of α-chloromalonates or nitromethane to 4-oxo-4-arylbutenoates **27** to give corresponding α-substituted ester adducts.[466] As an extension, pyrazolidinones were studied as alternative nucleophiles.[467] As presented in Scheme 203, the *N,N′*-dioxide ligand **L7** allowed the preparation of adducts **29a** and **29b** with good to excellent regio-, diastereo-, and enantioselectivies. One interesting feature of this reaction is the influence of the metal nature; scandium salts gave one enantiopur adduct, whereas the switch to yttrium yielded its enantiomer.



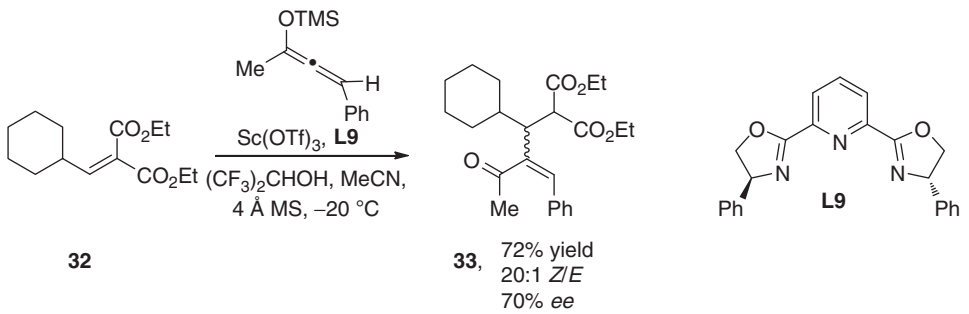
Scheme 203 Enantioselective Michael addition of pyrazolin-5-ones **28** to 4-oxo-4-arylbutenoates **27** mediated by *N,N′*-dioxide–scandium complex.

Following their efforts in the use of scandium(III) triflate complex of pyridine bis(oxazoline) **L8**, Desimoni et al. investigated asymmetric Friedel–Crafts alkylation of β,γ-unsaturated α-ketoesters **30** (Scheme 204).[468] Indole adducts **31** were isolated with high enantiomeric purity except when its position 2 was substituted (67% and 52% *ee* for respectively methyl and phenyl groups). *N,N′*-dioxide ligands were found to be also good ligands to perform Friedel–Crafts alkylations of indole with alkylidene malonate (scandium catalysis) or β,γ-unsaturated α-ketoesters (samarium or arsenic catalysis) in an enantioselective manner.[469]



Scheme 204 Asymmetric Friedel–Crafts alkylation mediated by scandium.

Scheidt and coworkers investigated silyloxyallenes as equivalents of α-acylvinyl anion to carry out conjugate addition to alkylidene malonates.[470] $Sc(OTf)_3$ showed a particularly good ability to catalyze this reaction. Moreover, this Lewis acid can be associated with a chiral ligand to achieve this transformation in an enantioselective manner (Scheme 205). (*R,R*)-Ph-pybox **L9** was found to be an attractive ligand because 70% *ee* could be reached during preliminary investigation.

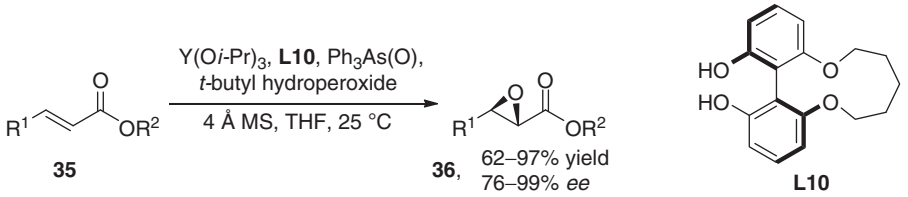


Scheme 205 Sc-promoted enantioselective addition of silyloxyallene to alkylidene malonate.

4.04.6.2.2 Epoxidation

Following his work on the development of asymmetric epoxidation of α,β-unsaturated carbonyl compounds,[452] Shibasaki was also interested in α,β-unsaturated ester substrates.[471] To build an efficient catalytic system, rare earth metals combined with various biaryldiol ligands were tested (Scheme 206). Yttrium(III) triflate exhibited clearly the best activity; dysprosium and gadolinium

equivalents provided also excellent enantioselectivities but lower yields. It has been observed that both chemical and optical yields were correlated with the Lewis acidity of rare earth elements to the exception of scandium. Biaryldiol **L10** allowed the preparation of numerous enantiopur α-ester epoxides.



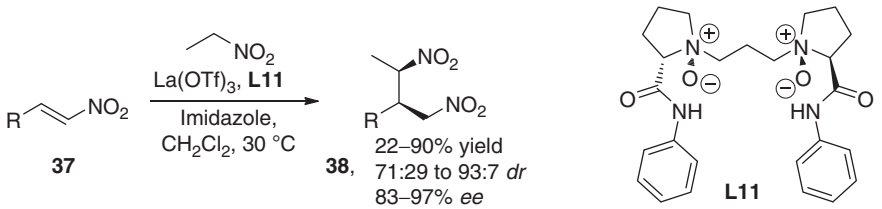
Scheme 206 Asymmetric epoxidation of α,β-unsaturated esters using yttrium-based catalyst.

4.04.6.2.3 Sulfa-Michael

$LaNa_3$tris(binaphthoxide) **C10** which was found efficient for the sulfa-Michael of various thiols to cyclic enones (Scheme 200) demonstrated also a good ability with other substrates: esters and thioesters.[460]

4.04.6.3 Nitroolefins

The conjugate addition of nitroalkanes to nitroalkenes as Michael acceptors represents a powerful method for the preparation of 1,3-dinitro compounds as precursors of a myriad of useful building blocks. However, this transformation is also challenging because both diastereo- and enantioselectivities need to be controlled. In 2008, Feng and coworkers explored this reaction using lanthanum(III) triflate with chiral *N*,*N*′-dioxide ligands (Scheme 207).[472] Treatment of nitroethane with nitroalkenes **37** in the presence of $La(OTf)_3$, **L11** and a catalytic amount of base – imidazole gave slightly better results than trialkylamines or potassium carbonate – afforded 1,3-dinitroalkanes **38** generally with good diastereoselectivity and excellent enantioselectivity of the major diastereomer. The example reported with nitropropane was as well remarkable with 92:8 *dr* and 95% *ee* for 65% yield.



Scheme 207 Asymmetric Michael addition of nitroethane to nitroolefins.

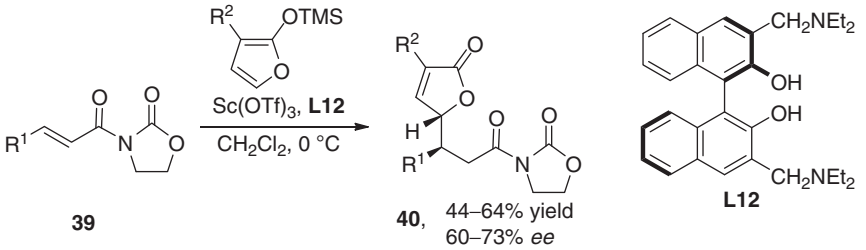
Recently, Zhang reported a heterotrimetallic Pd–Sm–Pd complex giving a good chiral induction for the enantioselective Friedel–Crafts alkylations of nitroolefins.[382]

4.04.6.4 α,β-Unsaturated Amides

Rare earth metal-catalyzed enantioselective addition to α,β-unsaturated lactames has not been reported so far. However, acyclic α,β-unsaturated amides, mainly 3-acryloyl-2-oxazolidinone derivatives **39** and acylpyrroles, were investigated for several addition reactions such as Michael additions of *C*-, *N*-, and *S*-nucleophiles and conjugate cyanation.

4.04.6.4.1 Addition of C-nucleophiles

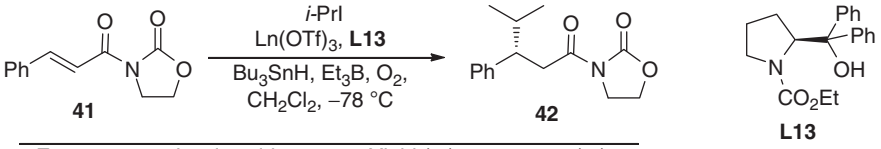
In 1997, Katsuki and coworkers examined the Michael addition of (trimethylsilyloxy)furans to oxazolidinone enoates **39** to prepare 4-substituted butenolides **40** which are subunits encountered in many natural products.[473] As depicted in Scheme 208, scandium(III) triflate combined with 3,3′-bis(diethylaminomethyl)1,1′-bi-2-naphtol **L12** allowed the preparation of compounds **40** as a unique diastereomer *anti* with low yields and moderate enantioselectivity. The addition in the reaction mixture of hexafluoroisopropanol improved reaction yields but came along with a slight decrease in *ee* values. This acidic alcohol favors enolate quenching and its low coordinating ability perturbs gently the scandium coordination sphere with a low alteration to the enantioselectivity. Of note, a catalytic system with $Cu(OTf)_2$ and bisoxazoline exhibited excellent enantioselectivity but moderate to good *anti*-selectivity. A similar system using chiral pyridine-bis(oxazoline) ligands was described by Suga.[474]



Scheme 208 Enantioselective Michael addition of (trimethylsilyloxy)furans to 3-acryloyl-2-oxazolidinone derivatives.

α,β-Unsaturated *N*-acylpyrroles are particularly good substrates for asymmetric Michael additions, as showed by Matsunaga and Shibasaki using lanthanum salt and linked-BINOL chiral ligands.[475]

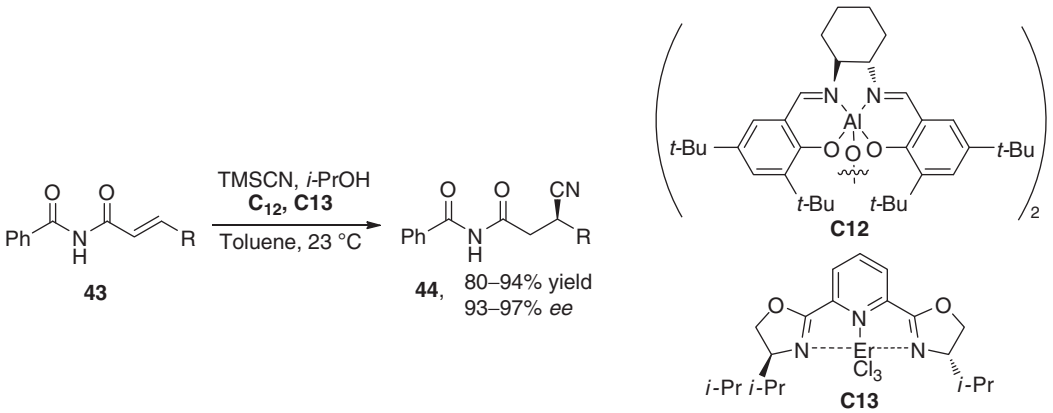
Following their effort to develop conjugate additions of nucleophilic radicals using chiral Lewis acids, Sibi et al. investigated lanthanide triflates because of their high strength and air and moisture stability.[476] Using the addition of iso-propyl radical (generated from *i*PrI) to α,β-unsaturated enoate **41** as model reaction, several lanthanide triflates were tested in association with (*S*)-proline derived alcohol **L13** (Scheme 209). The enantioselectivity was found to be dependent from the ionic radii of the lanthanide ion; ionic radii decrease from entries 1 to 6. Samarium allowed to reach the highest *ee* values (up to 92% *ee* using an optimized ligand and additives).



Entry	Lewis acid	Yield (%)	*ee* (%)
1	$La(OTf)_3$	88	64
2	$Nd(OTf)_3$	84	76
3	$Sm(OTf)_3$	84	79
4	$Eu(OTf)_3$	62	58
5	$Y(OTf)_3$	83	62
6	$Yb(OTf)_3$	87	39
7	$Hf(OTf)_4$	34	0

Scheme 209 Asymmetric conjugate radical addition using lanthanides.

The conjugate addition of cyanide to Michael acceptors was examined with substrates other than α,β-unsaturated ketones. For instance, in 2004, Jacobsen reported the conjugate cyanation of unsaturated imides **43** using cooperative dual catalysis (Scheme 210).[477] To reduce reaction time and catalyst loadings of salen aluminum complexes in conjugate cyanation, the addition of a second chiral catalyst capable of activating the cyanide was explored. Lanthanides which are known as cyanide activators, were tested successfully. Thus, a cooperative dual catalyst system with two chiral complexes (salen)aluminum **C12** and



Scheme 210 Enantioselective conjugate cyanation of unsaturated imides.

pyridine bis(oxazoline)erbium **C13** performed the conjugate addition of hydrogen cyanide to α,β-unsaturated imides **44** with excellent yields and enantioselectivities.

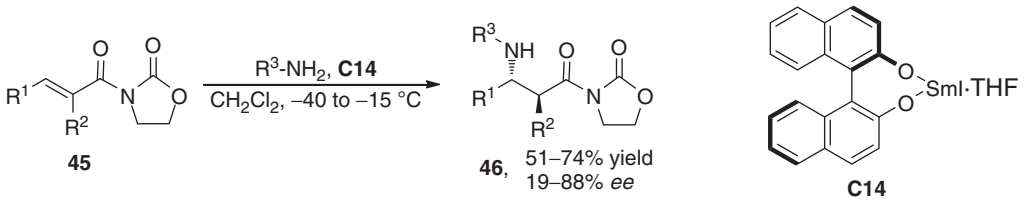
An extremely efficient system for enantioselective conjugate cyanation was developed by the group of Shibasaki using gadolinium salt and a phosphine oxide derived from D-glucose **L3** as chiral ligands. Before focusing on α,β-unsaturated ketones,[450] other Michael acceptors were tested.[478] Although benzylidenemalonate and 3-acryloyl-2-oxazolidinone derivatives **39** gave respectively poor and moderate enantioselectivities, α,β-unsaturated *N*-acylpyrroles allowed to reach high *ee* values (up to 98% *ee*).

4.04.6.4.2 Epoxidation

The enantioselective synthesis of aeruginosin 298-A and analogs, which is an equipotent thrombin and trypsin inhibitor, was achieved by Fukuta et al. using a lanthanum–BINOL complex-mediated asymmetric epoxidation of a α,β-unsaturated *N*-acylimidazole as key step.[479]

4.04.6.4.3 Aza-Michael

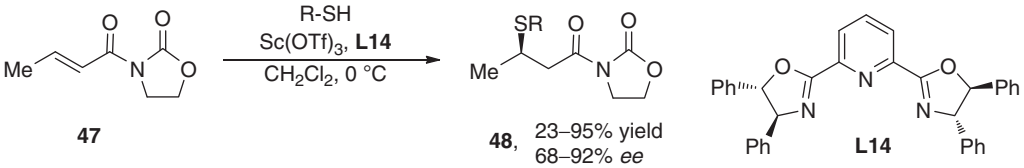
The aza-Michael addition of anilines and *O*-alkylhydroxylamines to 3-acryloyl-2-oxazolidinone derivatives **45** has been studied in details by Collin and coworkers using a samarium iodobinaphtoate catalyst **C14** (Scheme 211).[480] Adducts **46** were obtained with fluctuating yields and enantiomeric excesses as a function of the substrate and the nucleophile. Interestingly, an isoinversion effect has been noticed, with a maximum *ee* at −40 °C. Moreover, a NLE was observed, suggesting several active species. Aza-Michael additions of *O*-alkylhydroxylamines to α,β-unsaturated *N*-acylpyrroles was achieved with excellent optical purity of the adduct using the YLi_3tris(binaphthoxide) complex **C9** which was also competent for α,β-unsaturated ketones as substrates.[457] Other ligands such as pyridine-bis(oxazoline) were tested to carry out this reaction.[481] Despite good *ee* values, significant amounts of *N*-benzyloxyamides were obtained as by-products.



Scheme 211 Enantioselective aza-Michael addition catalyzed by samarium iodobinaphtoate.

4.04.6.4.4 Sulfa-Michael

To develop a robust catalytic system for the ACA of thiols to acyclic α,β-unsaturated carbonyl compounds, Koskinen investigated chiral pyridine-bis(oxazoline) ligands.[482] After the screening of several ligands, **L14** was found to give the best chiral induction for the addition of aryl- and alkylthiols to 3-crotonoyl-2-oxazolidinone **47** to afford **48** with *ee* up to 92% (Scheme 212).



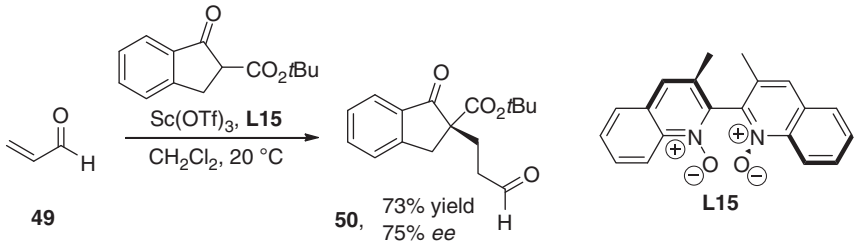
Scheme 212 Asymmetric sulfa-Michael addition catalyzed by scandium.

4.04.6.5 α,β-Unsaturated Aldehydes

Surprisingly, only one example of enantioselective addition to α,β-unsaturated aldehydes promoted by rare earth metals has been reported so far. In 2001, Nakajima reported the addition of *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate to acrolein **49** using a scandium(III) triflate in combination with chiral *N*,*N*′-dioxide ligand **L15** (Scheme 213).[442] Despite interesting chemical and optical yields, this substrate was not further investigated probably because of the necessity to convert adduct **50** into methyl ester analog to determine the yield and the enantiomeric excess.

4.04.6.6 Miscellaneous Michael Acceptors

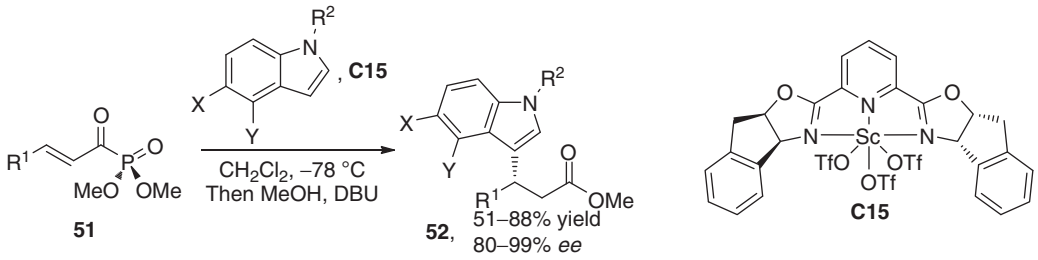
Having synthesized pyridine-bis(oxazolidinone)-scandium(III) complexes, Evans et al. were interested in using them as Lewis acid to promote addition of aromatic nucleophiles to electron-deficient alkenes.[483] Two particular types of Michael acceptors caught



49 50,

Scheme 213 Asymmetric Michael addition to acrolein **49**.

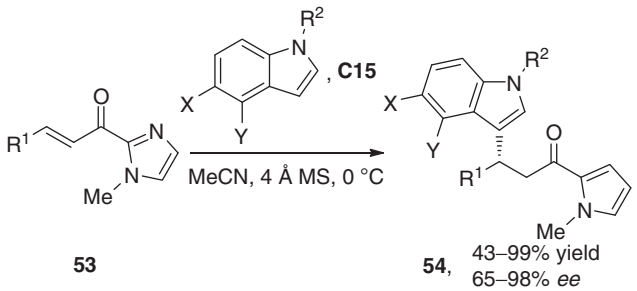
their attention for Friedel–Crafts alkylations of indoles: α,β-unsaturated acyl phosphonates **51** and α,β-unsaturated 2-acyl imidazoles **53**. As depicted in Scheme 214, complex **C15** exhibited good performances for the Friedel–Crafts alkylation of indole derivatives to substrates **51** in terms of both reactivity and enantioselectivity (up to 99% *ee*).[483a,d] One attractive feature of this reaction is the straightforward conversion of acyl phosphonate adducts into the corresponding esters **52** or amides by direct addition of alcohol or amine to the reaction mixture.



51 52,

Scheme 214 Enantioselective Friedel–Crafts alkylation to α,β-unsaturated acyl phosphonates **51**.

α,β-Unsaturated 2-acyl imidazoles **53** as substrates for Friedel–Crafts alkylation were studied for the first time by Evans using indole derivatives as nucleophiles.[483b,d] The scandium-based complex **C15** displayed both good activity and stereocontrol (Scheme 215). Variously substituted substrates **53** and indoles were well tolerated. It was noticed that *ee*s values were inversely proportional to catalyst loadings. Of note, pyrroles could be also used as nucleophiles at noncryogenic temperature to give adducts with high enantiopurity.[483c,d]



53 54,

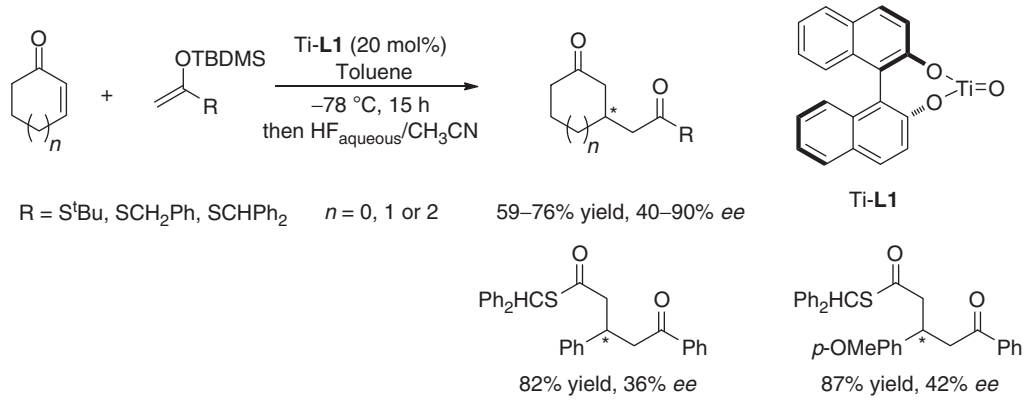
Scheme 215 Enantioselective Friedel–Crafts alkylation to α,β-unsaturated 2-acyl imidazoles **53**.

4.04.7 Ti/Zr/Hf Metal-Catalyzed Enantioselective Conjugate Addition

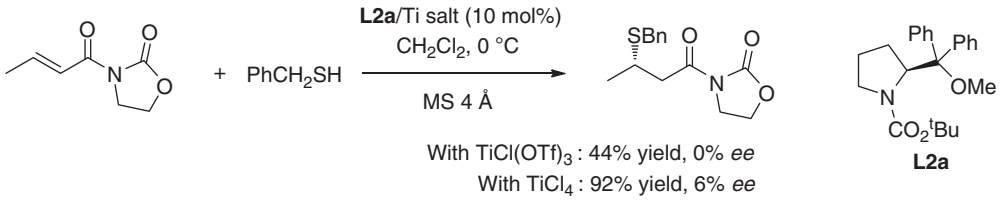
4.04.7.1 ACA Catalyzed by Ti-Complexes

The first report on ECA catalyzed by chiral titanium-based complexes was disclosed by Kobayashi et al. in early 1994.[484] In the presence of catalytic amount (20 mol%) of the oxo-titanium Lewis acid Ti-**L1** derived from (*R*)-binol **L1**, up to 90% of *ee* was reached for the 1,4-addition of silyl enol ethers to α,β-unsaturated cyclic enones (Scheme 216). Chalcone derivatives were also evaluated, affording the corresponding Michael adducts with lower enantiomeric excesses (36–42%).

Later, Kobayashi et al. examined the use of prolinol-based **L1**-titanium Lewis acids for the asymmetric Michael reactions of benzylthiol to the crotonyl oxazolidinone (Scheme 217).[485] However, the resulting Michael adduct was isolated in racemic form or with extremely low *ee* of 6%.

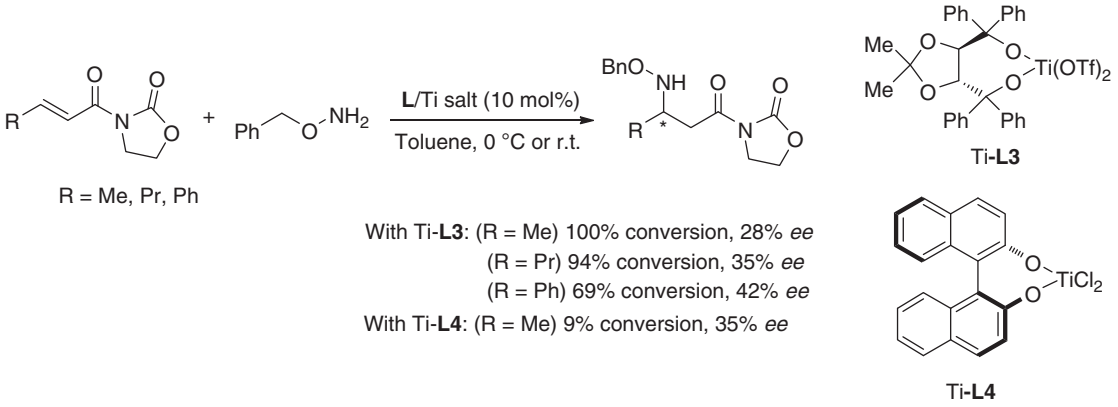


Scheme 216 BINOL-based oxo-titanium complex catalyzing the 1,4-addition of silyl enol ethers to cyclic and acyclic enones.



Scheme 217 Prolinol-based titanium Lewis acids catalyzing the 1,4-addition of benzylmercaptan to the crotonyl oxazolidinone.

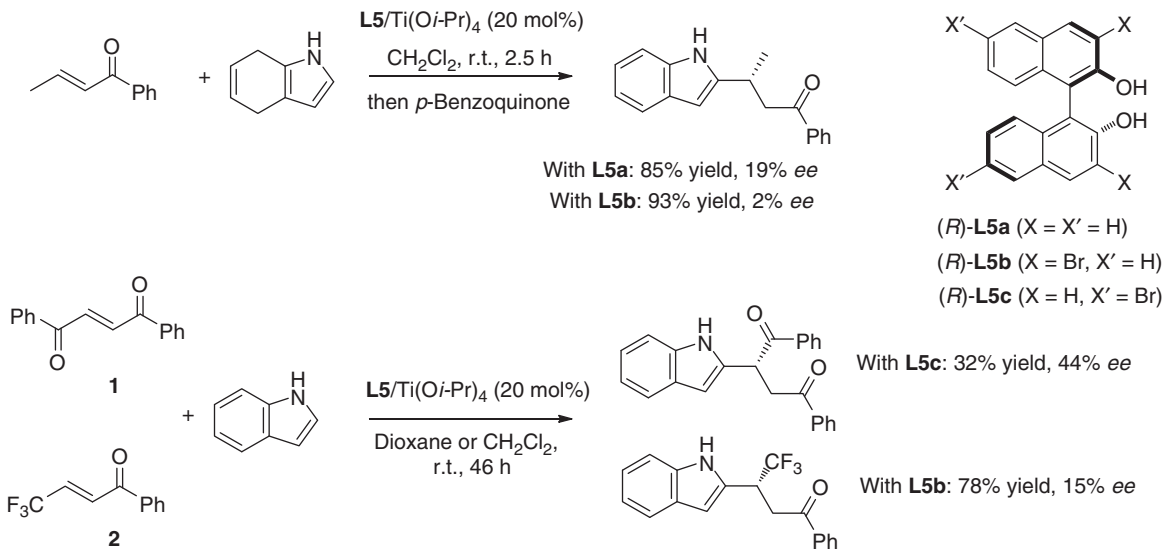
In 1996, Jørgensen and Falborg reported the Michael addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated 1,3-oxazolidinones catalyzed by TiX_2–TADDOLate (Ti-**L3**) and $TiCl_2$–BINOLate (Ti-**L4**) complexes (Scheme 218).[486] Good conversions of β-amino acid precursors with enantiomeric excesses up to 42% were obtained when 10 mol% of titanium catalysts was used.



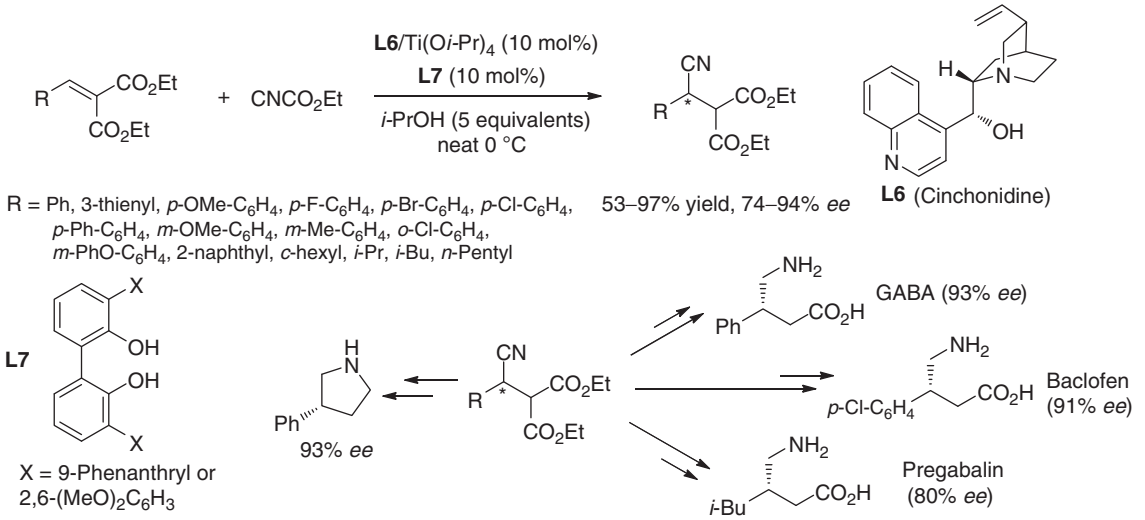
Scheme 218 Michael addition of *O*-benzylhydroxylamine to α,β-unsaturated *N*-acylated 1,3-oxazolidinones catalyzed by TiX_2–TADDOL and $TiCl_2$–BINOL complexes.

In 2007, Pedro and coworkers showed that chiral binol-type ligands **L5** in the presence of Ti(O*i*-Pr)$_4$ could catalyze the addition of indole derivatives to β-phenyl enones.[487] Despite high isolated yields, the Friedel–Craft adducts were obtained in a maximum of 19% of *ee* (Scheme 219). Extension to other Michael acceptors such as enediones **1**[488] or β-trifluoromethyl-enone **2**[489] was also unsuccessful, affording the corresponding adducts with low *ee*s of 44% and 15% *ee*, respectively (Scheme 218).

In 2010, Feng and coworkers reported a cinchonidine **L6**–titanium complex in the presence of achiral biphenol ligands **L7**-promoted cyanation of various arylidene- and alkylidene malonates (Scheme 220).[490] Up to 94% *ee* and 99% of yields were observed when a cyanide source of ethyl cyanoformate was used. Interestingly, the enantioenriched Michael adducts could be converted into valuable building blocks, such as pyrrolidine or γ-aminobutyric acids (GABA). However, the new developed titanium catalytic system remained unreactive toward nitrolefins or α,β-unsaturated esters.

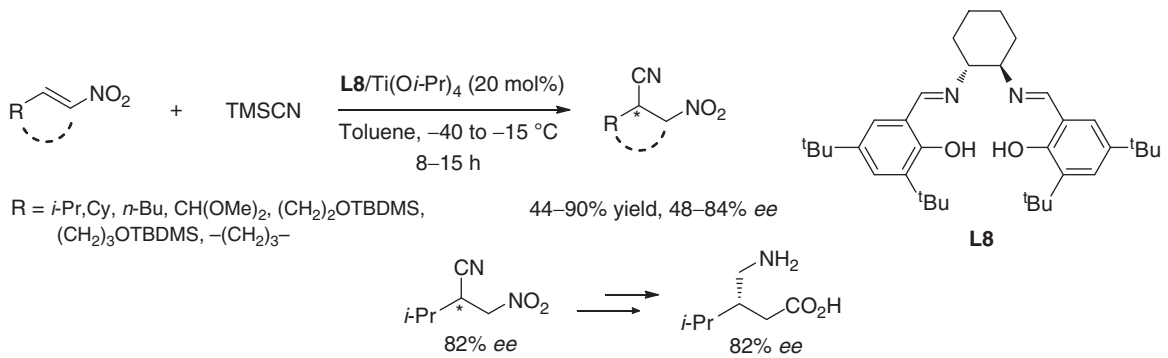


Scheme 219 Friedel–Crafts reaction promoted by $Ti(O\textit{i}\text{-}Pr)_4$ /chiral binol-based ligands.



Scheme 220 Enantioselective cyanation of various arylidene- and alkylidene malonates promoted by a cinchonidine-based titanium complex.

In front of this lack of reactivity toward nitroolefins, Wang and coworkers proposed in 2012 to use a salen–titanium complex for the Michael addition of TMSCN to various acyclic and cyclic nitroalkenes (Scheme 221).[491] By mixing 20 mol% of salen ligand

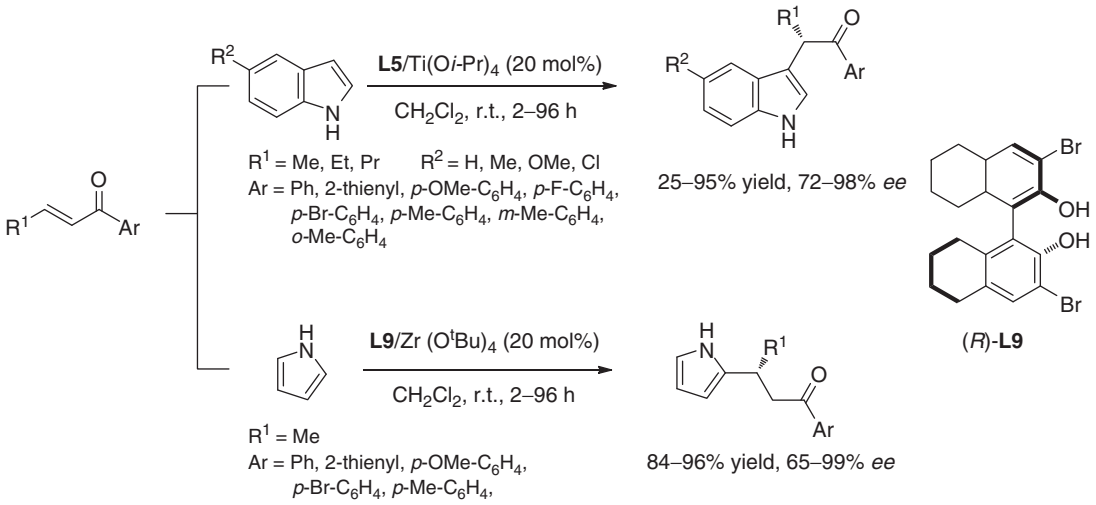


Scheme 221 Asymmetric conjugate cyanation of nitroolefins catalyzed by a salen-based titanium complex.

L8 and Ti(O*i*-Pr)$_4$, moderate to good yields (44–90%) and enantioselectivities up to 84% were reached. Thanks to the cyano and nitro groups, the resulting 1,4-adducts could be easily transformed into the corresponding highly desired β-amino acids without any alteration to enantioselectivity.

4.04.7.2 ACA Catalyzed by Zr-Complexes

The group of Pedro intensively studied Zirconium-based complexes for the enantioselective Friedel–Crafts alkylation of indole and pyrrole derivatives with α,β-unsaturated ketones. In 2007, Pedro showed that chiral binols **L5** and **L9** appeared the best ligands for this kind of conjugate additions (Scheme 222).[492] Therefore, the alkylation of various substituted indoles to enones catalyzed by Zr(O^{t}Bu)$_4$/(*R*)-**L5b** afforded the corresponding Michael adducts in moderate to excellent yields (25–95%) and enantioselectivities up to 98%. However, concerning pyrrole reagents, the tetrahydrogenated binol **L9** led to the best enantioinduction, reaching up to 99% *ee*.



Scheme 222 First asymmetric Friedel–Crafts reaction catalyzed by Zr(IV) complexes.

Later, the same group extended this efficient methodology to 4,5-dihydroindole[487] and also to other Michael acceptors such as enedione **1**, β-keto-enoates **3**[488] or β-trifluoromethyl-enones **4**,[488] affording the corresponding 1,4-adducts in moderate to good yields and remarkable *ee*s (up to 97%) (Scheme 223).

4.04.7.3 ACA Catalyzed by Hf-Complexes

Kobayashi and coworkers were the first to report the use of a chiral hafnium-based catalyst for a Michael reaction.[485] In 2001, these authors developed an efficient catalytic system by mixing Hf(OTf)$_4$ and chiral proline-derivative ligands **L2** to promote the enantioselective 1,4-addition of thiols to various 3-(2-alkenoyl)2-oxazolidinones (Scheme 224). The resulting Michael adducts were isolated in moderate to high yields (53–92%) with high enantiomeric excesses (up to 94%).

Based on this pioneering work, Katsuki and collaborators proposed in 2004 to develop a hafnium(salen) complex Hf-**L10** for the same transformation.[493] Low to good yields (10–90%) and similar high enantioselectivities were reached (up to 93%) (Scheme 224). Later, the group of Pedro reported an enantioselective Friedel–Crafts alkylation of indole derivatives with various Michael acceptors **5** and **2** catalyzed by Hf(OTf)$_4$ in the presence of binol-type ligand **L5**.[488,489] Good yields and *ee*s up to 94% were obtained for the resulting Michael adducts (Scheme 225).

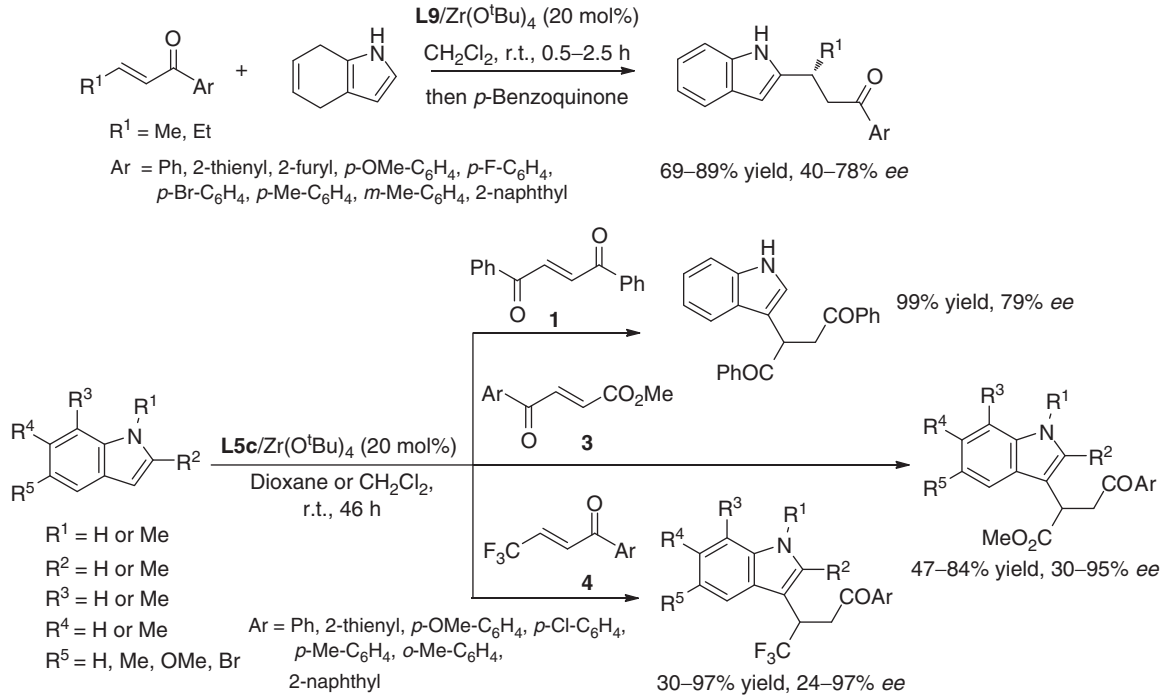
4.04.8 Mg/Zn Metal-Catalyzed Enantioselective Conjugate Addition

4.04.8.1 ACA Catalyzed by Chiral Magnesium-Based Complexes

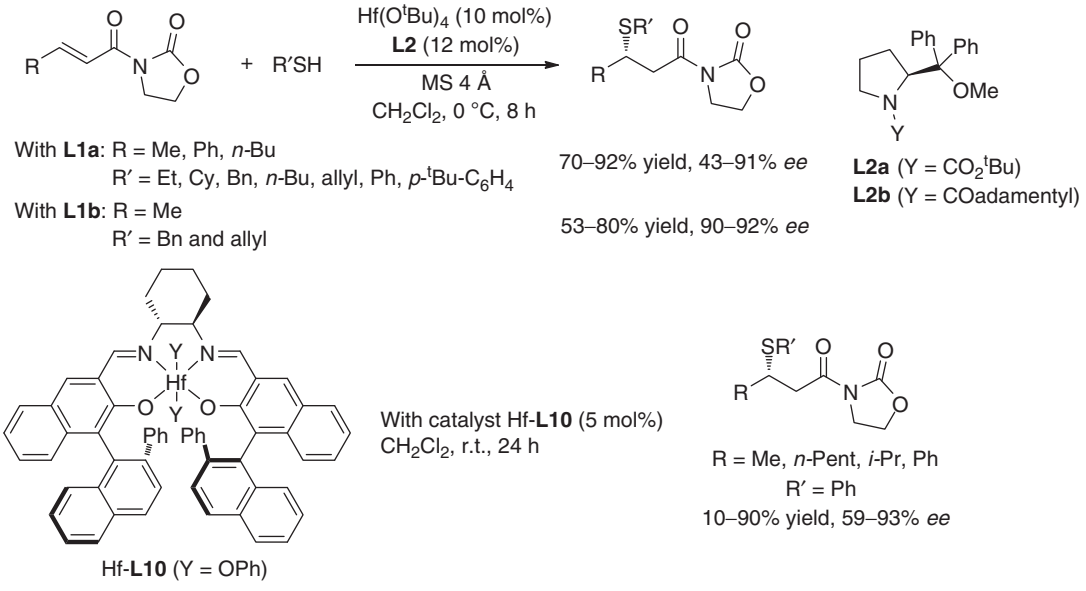
4.04.8.1.1 Addition of C-nucleophiles

4.04.8.1.1.1 Addition of malonate derivatives to nitroolefins and enones

In 1999, Ji et al. were the first to report the catalytic enantioselective Michael addition forming a C–C bond promoted by magnesium-based chiral complexes.[494] The conjugate addition of various malonates to nitroalkenes catalyzed by the bis-oxazoline ligand **L1** in the presence of magnesium-(II)-triflate led to the corresponding Michael adducts in excellent yields (88–95%) and



Scheme 223 Asymmetric Friedel–Crafts reaction of enediones, β-keto-enoate, and β-trifluoromethyl-enone catalyzed by Zr(IV)/binol complexes.

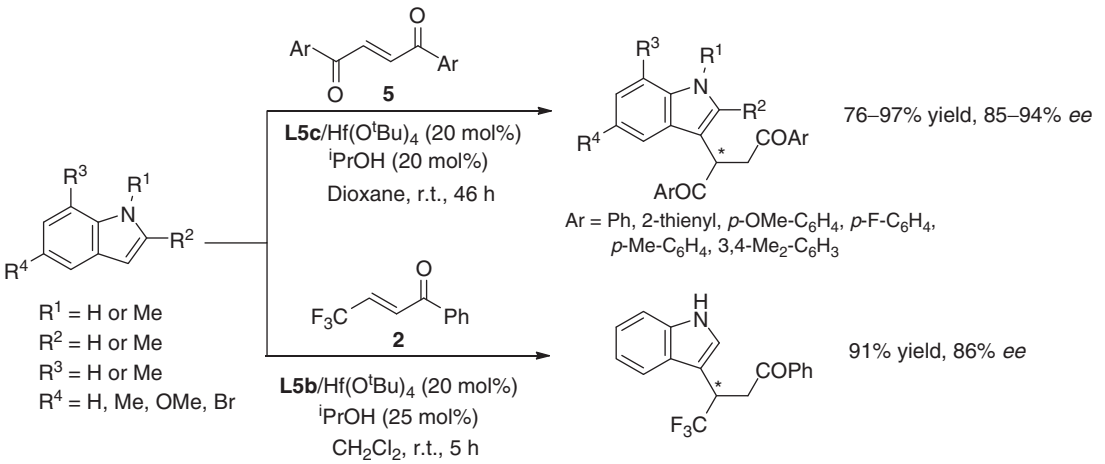


Scheme 224 First enantioselective conjugate addition catalyzed by a Hafnium-based complex.

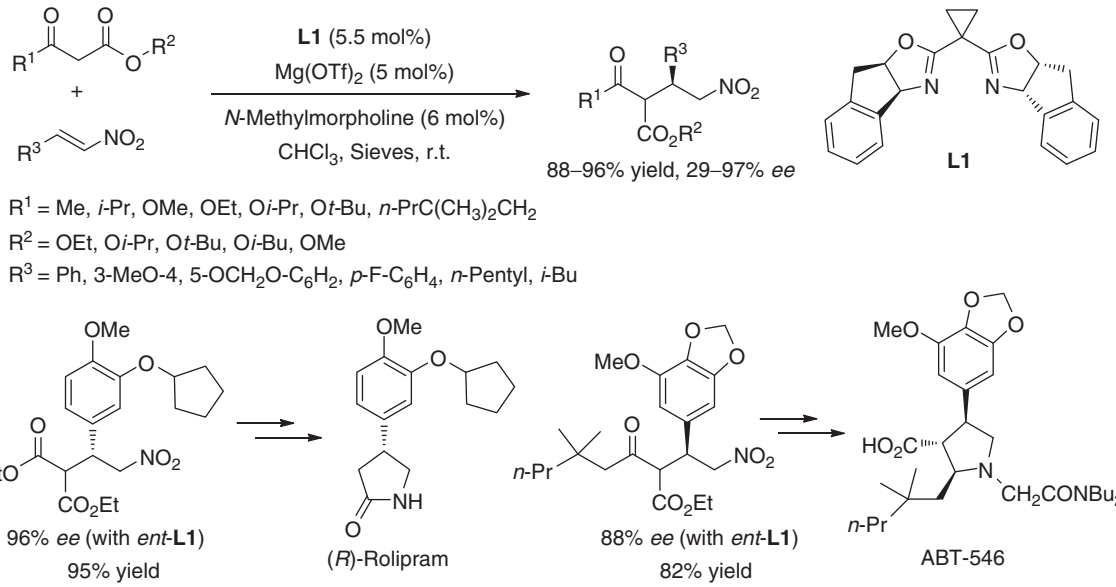
enantioselectivities up to 97% (Scheme 226). The scope was then extended to α-(hetero)alkyl-substituted malonates; nevertheless, the selectivities were lower, ranging from 50% to 84% *ee*.[495] Furthermore, this efficient methodology was then applied to the asymmetric total synthesis of endothelin-A antagonist ABT-546 and the antidepressant (*R*)-rolipram.

Later, Nichols et al. proposed to use the Ji's **L1**-Mg(OTf)$_2$ catalytic system for the addition of α-substituted malonates to various aromatic nitro-olefines to synthesize valuable pyrrolidine-based PDE4 inhibitors (Scheme 227).[496] Interestingly, the resulting Michael adducts were obtained in excellent yields (77–99%) and moderate to high *ee*s (44–99%). Remarkably, the synthesis of the PDE4 inhibitor IC86518 was done on the kilogram scale.

In 2002, Jackson and coworkers disclosed the conjugate addition of dibenzylmalonate to cyclic enones catalyzed by tartrate-based magnesium catalysts (Scheme 228).[497] A maximum of 58% of enantiomeric excess was reached with ligand **L2a** during the



Scheme 225 Enantioselective Friedel–Crafts reaction catalyzed by Hafnium/binol complexes.



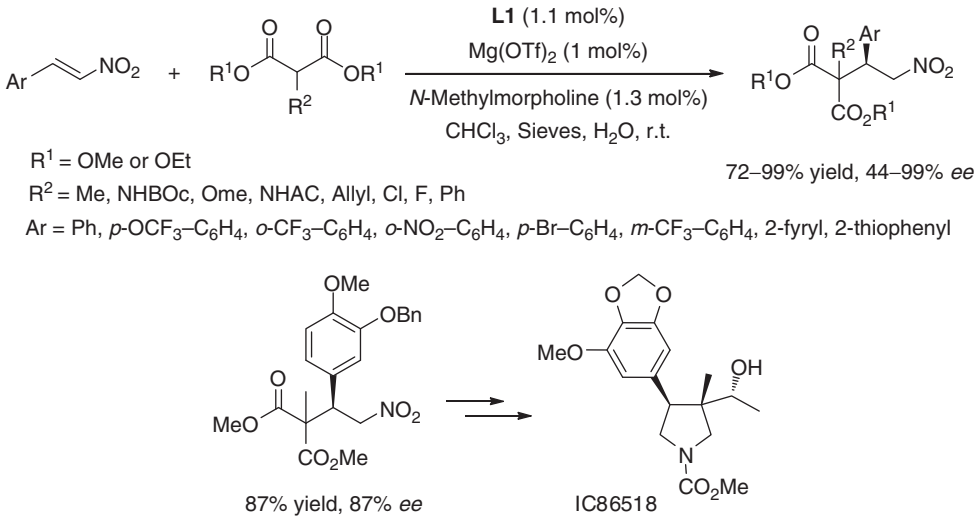
Scheme 226 First catalytic enantioselective Michael addition promoted by magnesium-based chiral complexes and related total synthesis of active pharmaceutical ingredients.

addition involving cyclohexenone, whereas lower selectivities were observed with cyclopentenone (50% with **L2b**) and cycloheptenone (39% with **L2c**). In 2007, a significant improvement in enantioselectivity for this transformation was reported by Kantam et al. with the use of nanocrystalline MgO in the presence of chiral 1,2-diphenylethylene diamine **L3**.[498] Up to 96% and 85% *ee* were observed for the addition of malonate derivatives to cyclic enones and the chalcone, respectively (Scheme 227).

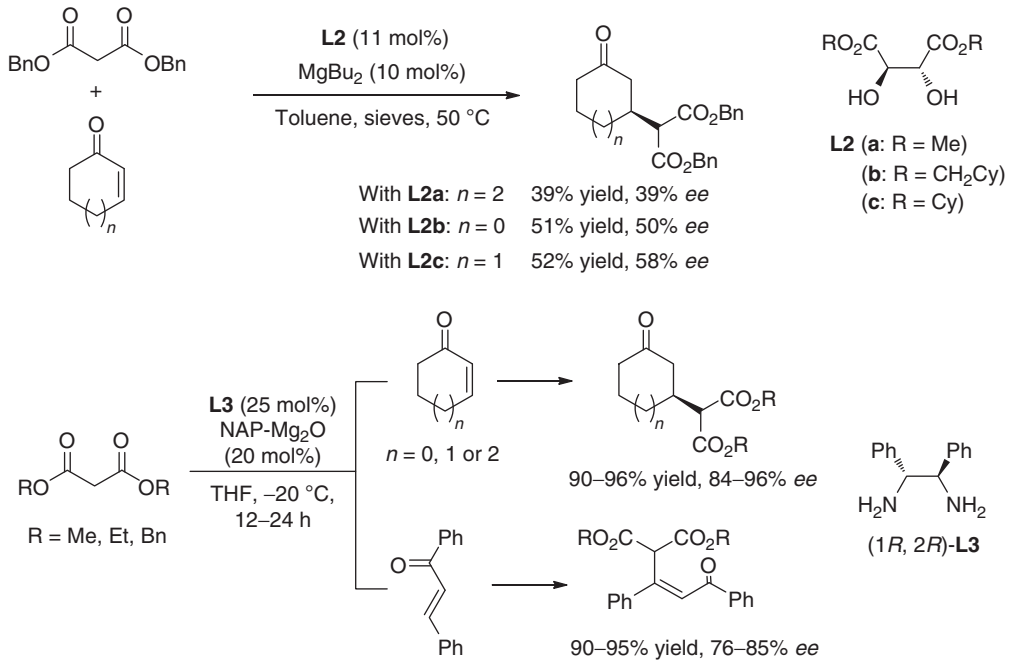
4.04.8.1.1.2 Miscellaneous C-nucleophiles

In 2006, Palomo et al. disclosed the catalytic enantioselective Michael addition of nitromethane to α-hydroxy enones promoted by the $Mg(OTf)_2$/bisoxazoline **L1** complex initially developed by Ji and Barnes (Scheme 229).[499] Remarkably, good to high enantiomeric excesses could be reached (up to 94%) for a wide range of Michael adducts, which were isolated in moderate to excellent yields (56–93%). Furthermore, the resulting adducts were easily oxidized into the corresponding γ-nitro carboxylic acid or aldehydes. However, this catalytic system was not enantioselective in relation to other α,β-unsaturated carboxylic acid surrogates such as crotonyl oxazolidinone or alkylidenemalonates.

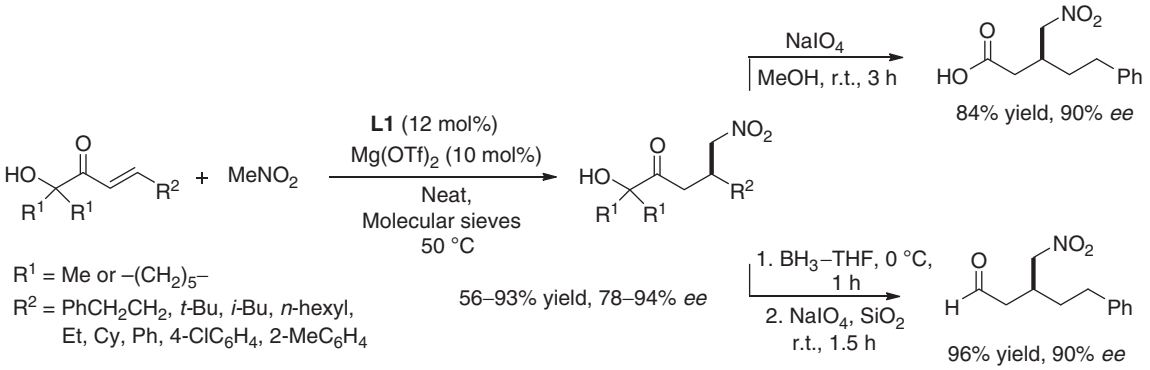
Recently, Luo and coworkers disclosed the use of a binary chiral phosphoric acid **L4**/MgF_2 complex to catalyze the enantioselective Friedel–Crafts addition of phenols to β,γ-unsaturated α-ketoesters.[500] Remarkably, the resulting Michael adducts were isolated in moderate to good yields (up 82%) and excellent *ee*s reaching up to 99% (Scheme 230). This methodology was then



Scheme 227 Magnesium-catalyzed enantioselective conjugate addition of α-substituted malonates to nitro-olefines.

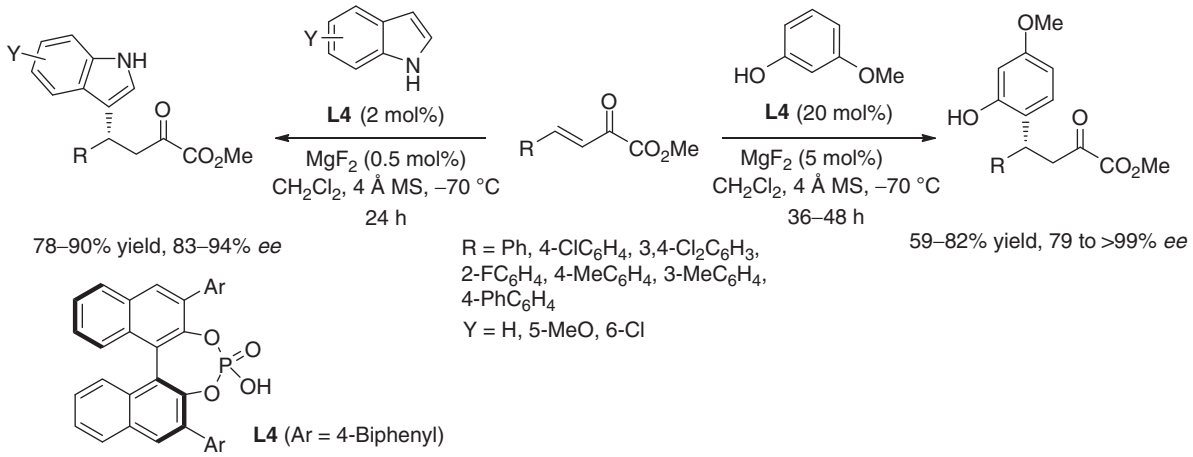


Scheme 228 Magnesium-catalyzed enantioselective conjugate addition of malonate derivatives to enones.



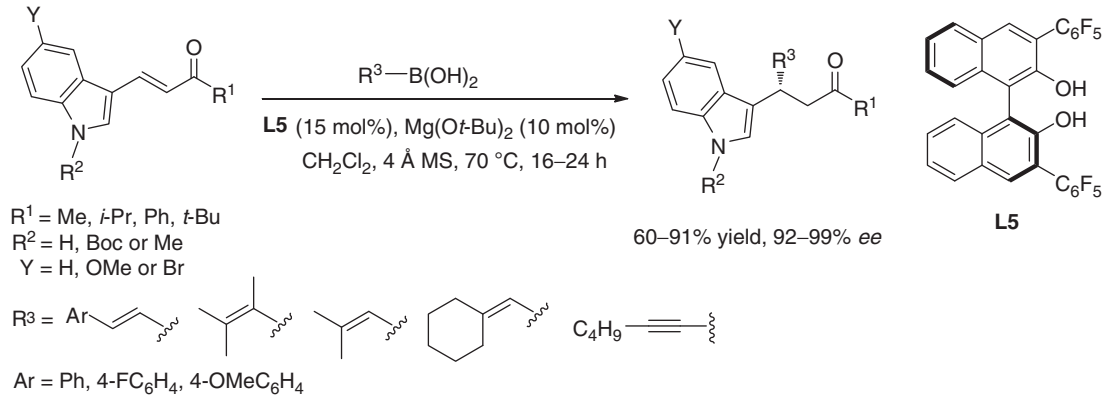
Scheme 229 Magnesium-catalyzed enantioselective conjugate addition of nitromethane to α-hydroxy enones.

extended to indole nucleophiles. Interestingly, 0.5 mol% of magnesium salts sufficed to catalyze the reaction, leading to a wide range of desired 1,4-adducts in good yields (up to 90%) with 82–94% *ee*.



Scheme 230 Enantioselective Friedel–Crafts addition of phenols and indoles to β,γ-unsaturated α-ketoesters promoted by a binary chiral phosphoric acid **L4**/MgF_2 complex.

Lastly, in 2011, May and coworkers reported the enantioselective Michael addition of alkenyl- and alkynyl- boronic acids to indole-appended aliphatic enones catalyzed by mixing binol derivative ligand **L5** and $Mg(O\text{-}t\text{-}Bu)_2Mg$ salt.[501] A wide range of enantioenriched α-branched indole derivatives was synthetized through this methodology with good isolated yields (70–91%) and remarkable *ee*s (typically > 92%) (Scheme 231).

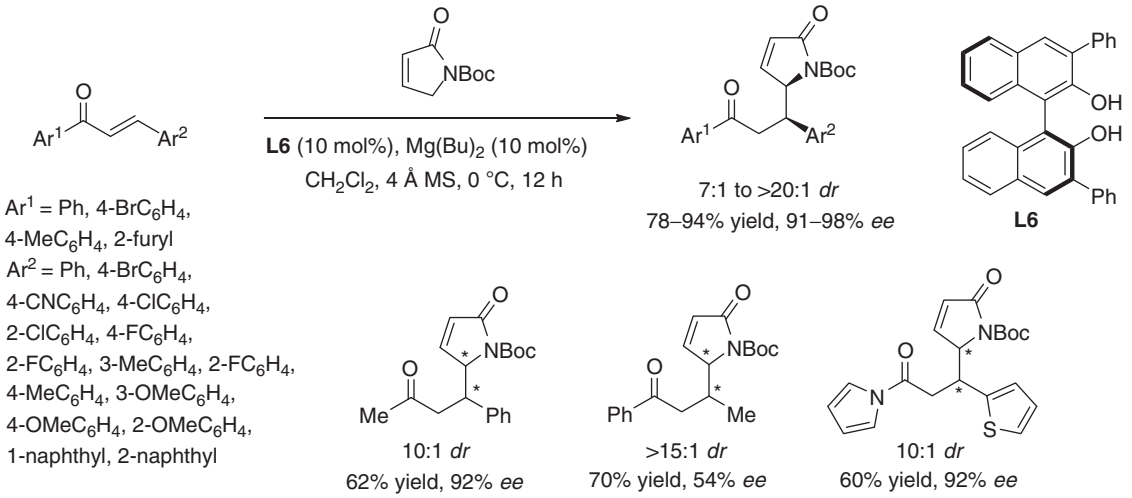


Scheme 231 Magnesium-catalyzed enantioselective conjugate addition of alkenyl- and alkynyl- boronic acids to indole-appended aliphatic enones.

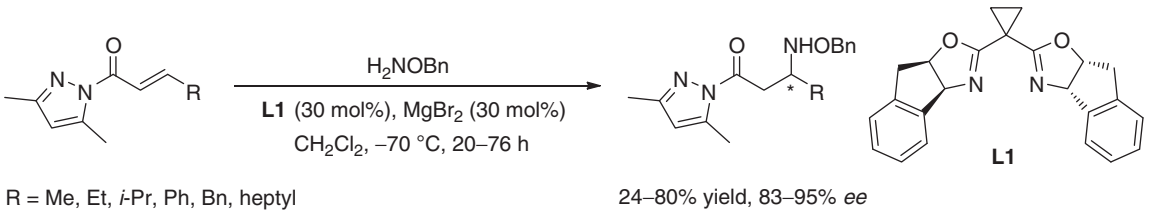
In the meantime, Wang and coworkers also proposed the use of chiral binol-based ligand **L6** in the presence of magnesium salts to catalyze the direct asymmetric vinylogous 1,4-addition of α,β-unsaturated γ-butyrolactam to various aliphatic Michael acceptors.[502] As depicted in Scheme 232, the catalytic Mg-based system was able to provide a wide range of Michael products with high diastereoselectivities (up to 20:1) and excellent enantioselectivities (91–98%), expected for the crotyl 1-phenyl-enone (54% *ee*). Moreover, this methodology was also efficient toward α,β-unsaturated *N*-acylpyrroles, which could be easily converted into corresponding ester, acid, or amide derivatives.

4.04.8.1.2 Addition of hetero-nucleophiles

Sibi et al. have intensively studied the ECA of hydroxylamine to various Michael acceptors catalyzed by magnesium-based Lewis acid. In 1998, they reported for the first time that catalytic amount (30 mol%) of bis-oxazoline ligand **L1** and magnesium-(II)-bromide were able to promote the addition of *O*-benzylhydroxylamine to α,β-unsaturated amides.[503] The corresponding Michael adducts were isolated in moderate to good yields (24–80%) with high enantioselectivities (83–95% *ee*) (Scheme 233). At lower catalyst loading (10 mol%), the enantioselectivities were slightly altered (57–87%).

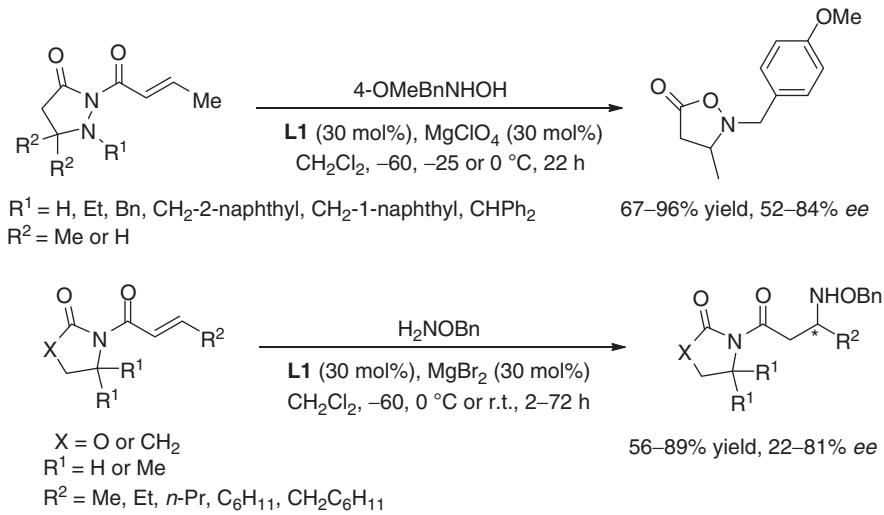


Scheme 232 Magnesium-catalyzed direct asymmetric vinylogous 1,4-addition of α,β-unsaturated γ-butyrolactam to various aliphatic Michael acceptors.



Scheme 233 Pioneering developments of asymmetric aza-Michael addition catalyzed by chiral bis-oxazoline-based magnesium complexes.

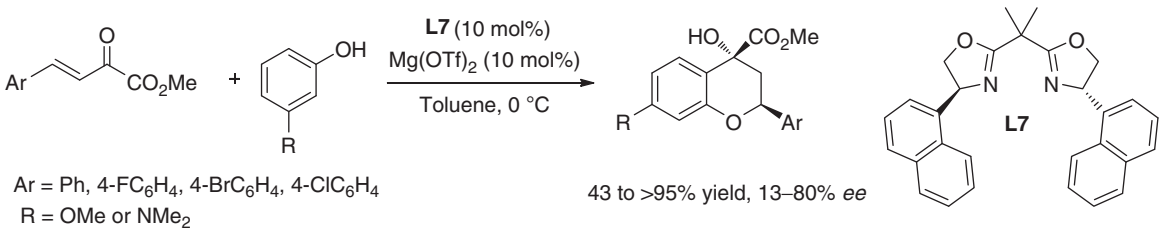
Three years later, the same group extended this methodology to other unsaturated amides such as pyrazolidinone,[504] oxazolidinone, and pyrrolidinone acrylamides.[505] Moderate to good yields were generally observed with enantioselectivities ranging from 22% to 84% (Scheme 234).



Scheme 234 Extension of Sibi's methodology to pyrazolidinone, oxazolidinone, and pyrrolidinone acrylamides.

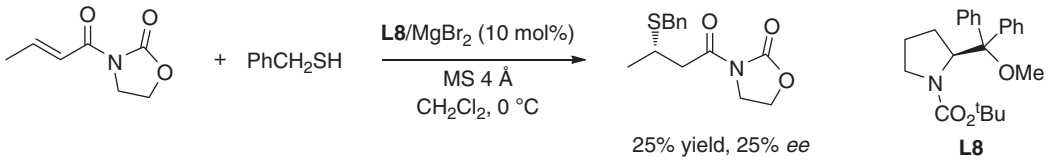
To the best of our knowledge, only one example was reported for the asymmetric oxa-Michael addition promoted by chiral magnesium-based complexes. Rutjes and coworkers developed in 2003 an efficient tandem reaction involving the oxa-Michael addition of phenols to β,γ-unsaturated α-ketoesters, followed by a Friedel–Crafts alkylation.[506] Through this tandem catalytic

process promoted by $Mg(OTf)_2$/bis-oxazoline **L7**, few optically active chromanes were isolated in moderate to excellent yields (43 to >95%) with enantioselectivities ranging from 13% to 80% (Scheme 235). The synthesis of tetrahydroquinolines was also attempted using this catalytic process; however, only racemic products were formed.



Scheme 235 First asymmetric oxa-Michael addition promoted by chiral magnesium-based complexes, followed by a Friedel–Crafts alkylation: synthesis of optically active chromanes.

Finally, one example of enantioselective thio-Michael addition catalyzed by a chiral Mg complex was disclosed by Kobayashi et al. in 2001.[485] To this end, the authors evaluated the combination of a prolinol-derived ligand and $MgBr_2$ to catalyze the addition of benzylthiol to 3-crotonoyl-2-oxazolidinone. Unfortunately, the resulting Michael adduct was isolated in poor yield and low enantioselectivity (Scheme 236).



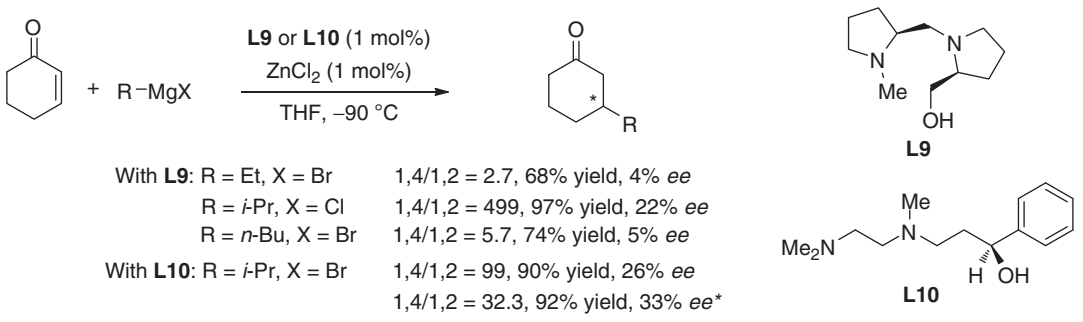
Scheme 236 First attempt of asymmetric thio-Michael addition promoted by a chiral magnesium-based complex.

4.04.8.2 ACA Catalyzed by Chiral Zinc-Based Complexes

4.04.8.2.1 Addition of C-nucleophiles

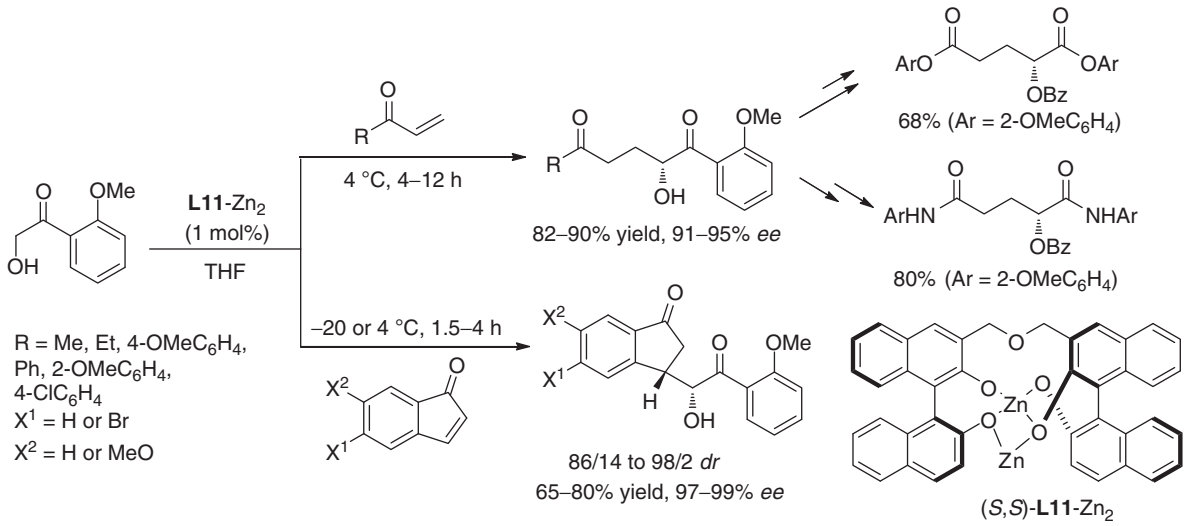
4.04.8.2.1.1 ACA of α,β-unsaturated enones

The first ECA catalyzed by chiral zinc-based complexes was disclosed by Feringa and Jansen in 1990.[507] In this study, a wide range of chiral ligands (20) in association with $ZnCl_2$ was screened for the addition of isopropyl-derived Grignard reagents to 2-cyclohexenone. The resulting 1,4-adduct was isolated in good to excellent yields (83–99%) with high chemo- and regioselectivities (1,4/1,2 ratios up to 499) and modest enantioselectivities (up to 33%). The ligand **L9** appeared the most regioselective one, whereas the highest *ee* was reached with **L10** (Scheme 237). During these seminal works, several factors were examined (ligand, solvent, counterions, order, and rates of addition, temperature, nature of the Grignard reagent), allowing highlighting their significant influence on both the regio- and enantioselectivity of the Michael addition. The scope was extended to ethyl and *n*-butyl organomagnesium reagents; however, the *ee*s remained extremely low (4–5%).



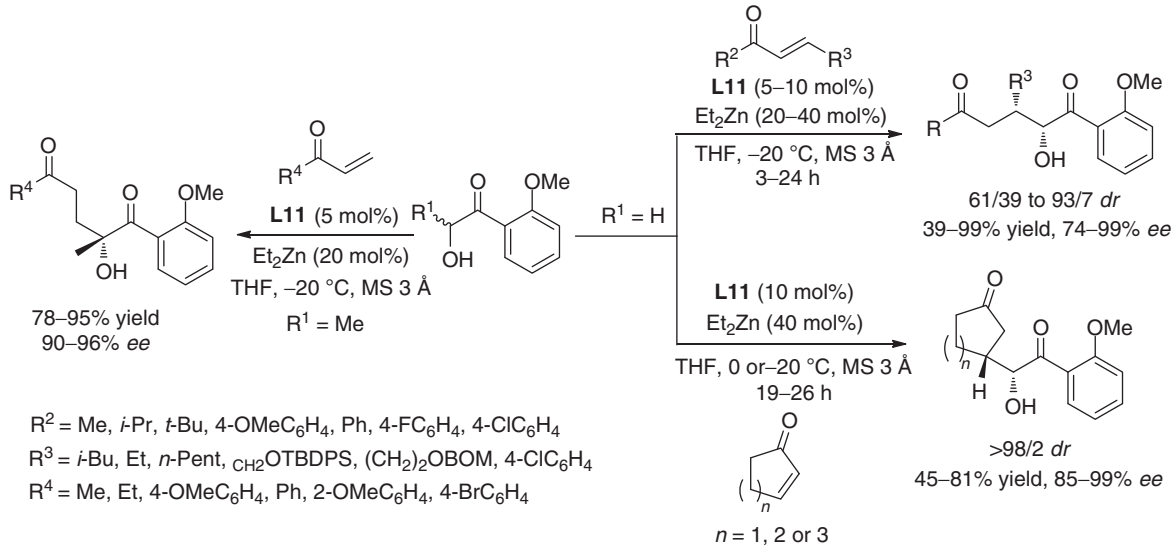
Scheme 237 First development of asymmetric Michael addition catalyzed by chiral zinc-based complexes.

Ten years later, Shibasaki and coworkers described the enantioselective Michael addition of 2-hydroxy-2′-methoxyacetophenone to various cyclic and acyclic α,β-unsaturated enones promoted by a bimetallic Zn–Zn-linked BINOL complex **L11**-Zn_2.[508] The resulting 2-hydroxy-1,5-diketones were isolated in good yields (up to 90%) with remarkable enantioselectivities (up to 99%). Interestingly, these optically active 1,4-adducts could be easily converted to highly desirable esters and amides via a Baeyer–Villiger oxidation or a Beckmann rearrangement (Scheme 238).



Scheme 238 Enantioselective Michael addition of 2-hydroxyketone to α,β-enones promoted by a bimetallic Zn–Zn-linked BINOL complex.

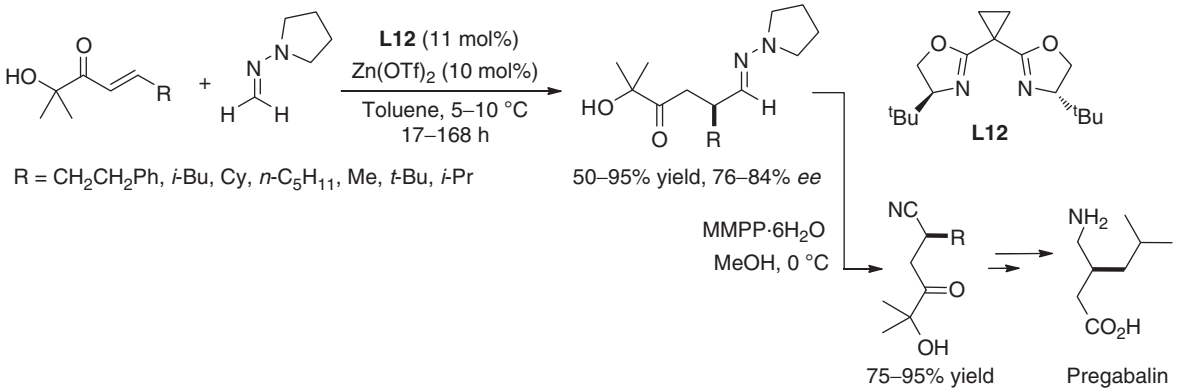
Later, the same authors proposed a slight modification of this methodology to improve the enantioselectivities and also to extend the scope to various β-substituted cyclic and acyclic enones (Scheme 239).[509] By mixing the linked BINOL **L11** and Et_2Zn in a 1/4 ratio, the second generation of catalytic system was effective for various β-substituted acyclic enones to afford Michael adducts in moderate to excellent yields (39–99%), high diastereoselectivities (61/39 to 93/7), and high enantioselectivities (up to 97%). Moreover, similar good results were also reached with five-, six-, and seven-membered cyclic enones ($dr > 98/2$, 45–81% yield, 85–99% *ee*). Remarkably, the new catalytic system was also efficient for Michael additions of 2-hydroxy-2′-methoxypropiophenone to generate an optically active quaternary stereogenic center in good yields (78–95%) with high *ee*s (up to 96%).



Scheme 239 Extended scope of Michael addition of 2-hydroxyketone to β-substituted enones catalyzed by a Et_2Zn-linked BINOL complex.

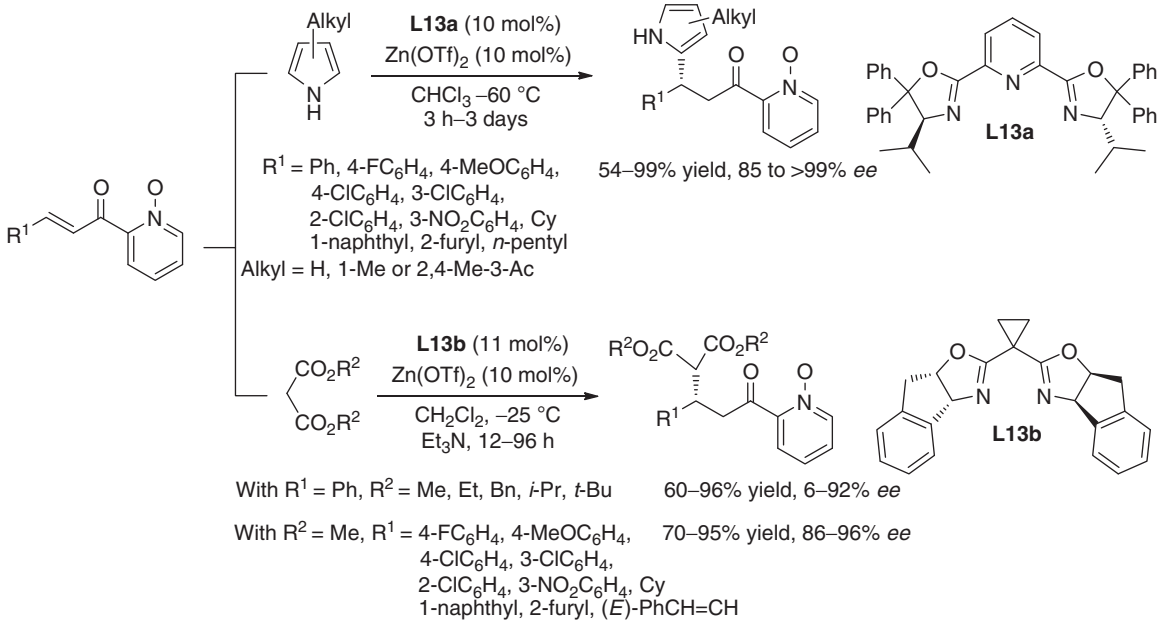
In 2007, Lassaletta and Fernandez evaluated the activation of α-hydroxy enones by $Zn(OTf)_2$ salt in the presence of chiral bisoxazoline ligand **L12** to catalyze the asymmetric Michael addition of 1-methyleneamino pyrrolidine as C-nucleophile.[510]

Moderate to good yields (50–95%) and high enantioselectivities (up to 84%) were observed (Scheme 240). Additionally, the potential of this methodology was illustrated through the synthesis of optically active β-cyano acids, which are direct precursors of bioactive GABAs, such as pregabalin.



Scheme 240 Zn-catalyzed asymmetric Michael addition of *N,N*-dialkylhydrazones to α-hydroxy enones.

Recently, Singh et al. also proposed the use of chiral bisoxazoline–$Zn(OTf)_2$ complexes for the catalytic Friedel–Crafts alkylation of pyrroles to 2-enoylpyridine *N*-oxide-based Michael acceptors (Scheme 241).[511] Among a small library of chiral bisoxazoline ligands, the PyBox **L13a** was the highest selective ligand, affording the alkylated-pyrroles in good to high yields (71–99%) and remarkable *ee*s (85 to >99%). One year later, this zinc-mediated methodology was then extended to malonate nucleophiles using the structurally modified bis-oxazoline ligand **L13b**.[512] The 1,4-adducts were obtained in good to high yields (60–96%) and remarkable *ee*s (up to 96%), except for sterically demanding substrates ($R^1 = t$-Bu) where no product was observed even after prolonged reaction times (Scheme 240).

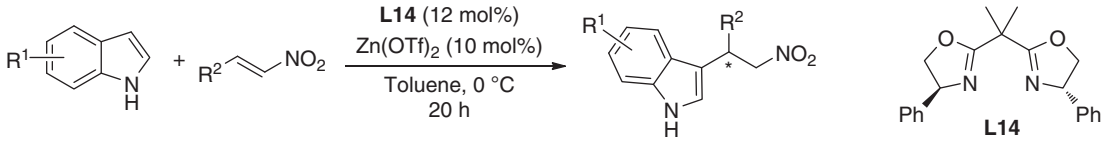


Scheme 241 Enantioselective conjugate addition of pyrroles and malonates to 2-enoylpyridine *N*-oxides catalyzed by chiral bisoxazoline-$Zn(OTf)_2$ complexes.

4.04.8.2.1.2 ACA of nitroolefins

Nitroolefins were intensively studied in zinc-promoted catalytic ECA of C-nucleophiles, notably for the asymmetric Friedel–Crafts alkylation involving indoles, pyrroles, and furanes. The first example was disclosed by Zhou and coworkers in early 2006.[513] They developed a catalytic system from the chiral bisoxazoline **L14** and $Zn(OTf)_2$ salt, which was able to catalyze efficiently the addition

of indole derivatives to various nitroalkenes (Scheme 242). The corresponding nitroalkylated indoles were synthesized in excellent yields (57–98%) and high enantioselectivities (up to 90%).

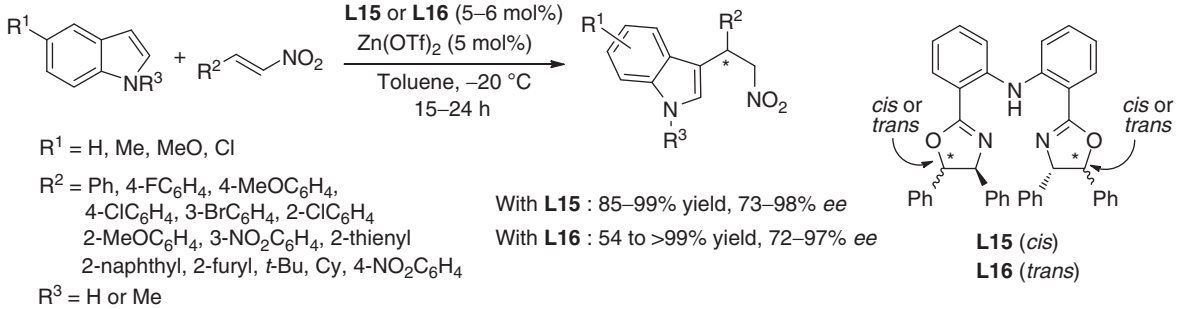


With R^1 = H, R^2 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-thienyl, 1-naphthyl, 2-furyl, *n*-propyl — 57–98% yield, 70–90% *ee*

With R^2 = Ph, R^1 = 1-Me, 2-Me, 5-OMe, 5-Br — 62–98% yield, 21–80% *ee*

Scheme 242 First enantioselective Friedel–Crafts alkylation of indoles to nitroalkenes catalyzed by chiral bisoxazoline-Zn(OTf)$_2$ complexes.

In the meantime, Du and coworkers reported several studies on this kind of Friedel–Crafts transformation catalyzed by bisoxazoline-modified ligands. By designing a bifunctional tridentate bisoxazoline **L15**-Zn(OTf)$_2$ catalyst, both yields and selectivities were improved, reaching up to 98% *ee* (Scheme 243).[514] Later, a structural modification of the tethered ligand (i.e., *trans*-diphenyl substitution, **L16**) in combination with new reaction conditions (−20 °C) allowed reaching higher reactivity and enantioselectivities in most cases (99% of yield, up to 97% *ee*).[515] In 2007, this methodology was then successfully extended to the methoxyfuran for the first time.[516] Good yields and excellent enantioselectivities (up to 96%) were reached for most aromatic and heteroaromatic nitroolefins. Finally, pyrrole derivatives were also examined by employing modified ligand **L17**, which afforded the corresponding Michael adducts in 42–91% of isolated yields and low to excellent *ee*s (up to 91%).[515]



R^1 = H, Me, MeO, Cl

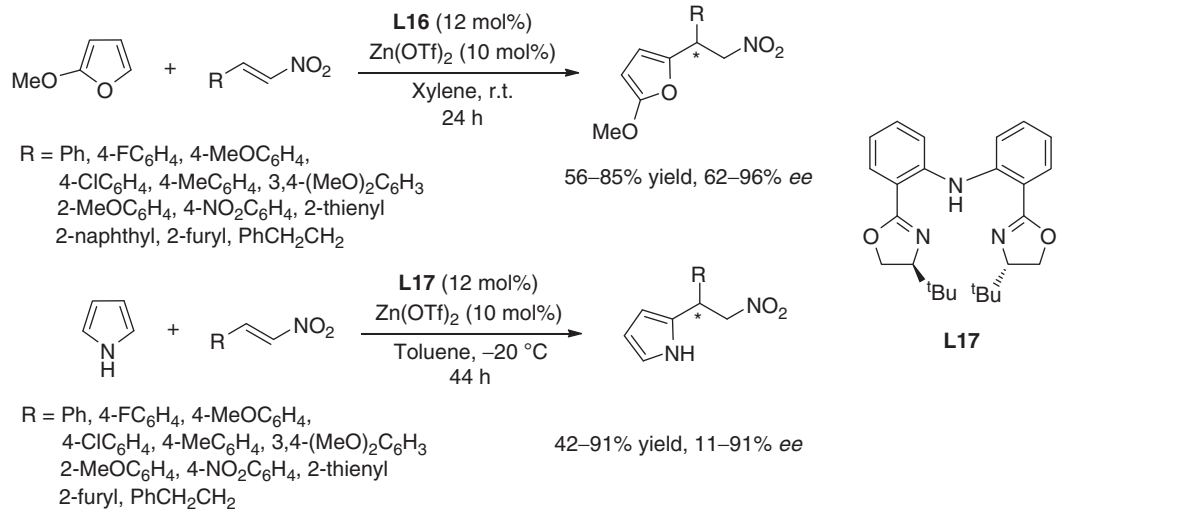
R^2 = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-BrC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$, 3-$NO_2C_6H_4$, 2-thienyl, 2-naphthyl, 2-furyl, *t*-Bu, Cy, 4-$NO_2C_6H_4$

R^3 = H or Me

With **L15** : 85–99% yield, 73–98% *ee*

With **L16** : 54 to >99% yield, 72–97% *ee*

L15 (*cis*)
L16 (*trans*)



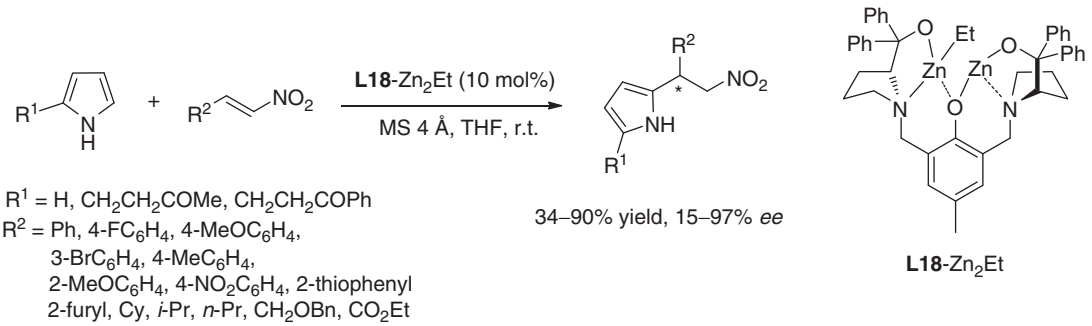
R = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 2-naphthyl, 2-furyl, $PhCH_2CH_2$ — 56–85% yield, 62–96% *ee*

R = Ph, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 3,4-$(MeO)_2C_6H_3$, 2-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl, $PhCH_2CH_2$ — 42–91% yield, 11–91% *ee*

Scheme 243 Asymmetric Friedel–Crafts alkylations of indoles, methoxyfuran, and pyrrole derivatives to nitroalkenes promoted by chiral bifunctional tridentate bisoxazoline-Zn(OTf)$_2$ catalysts.

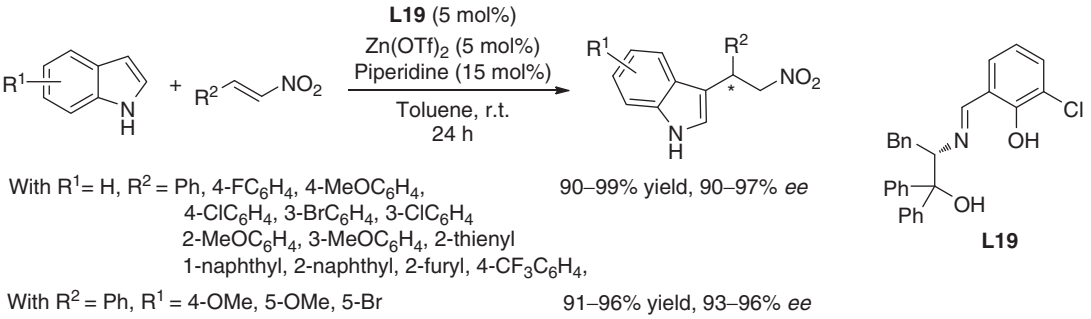
Recently, the same authors proposed an immobilized version of their zinc-based catalytic system by anchoring the bisoxazoline ligand **L15** onto dendrimeric polymers.[517] Interestingly, the new supported catalytic material was able to provide similar high reactivity and selectivity toward various substrates. Moreover, an excellent accumulative yield over five cycles of reuse (93–99%) was observed for the addition of indole to *β*-nitrostyrene without any alteration to enantioselectivity (92–93% *ee*).

Asymmetric Friedel–Crafts alkylation of unprotected pyrroles to nitroalkenes using a dinuclear zinc catalyst **L18**-Zn_2Et was examined by Trost and Müller in 2008.[518] As depicted in Scheme 244, various enantioenriched alkylated-pyrroles, including 2,5-disubstituted pyrroles, were produced in good yields (up to 92%) with moderate to high enantioselectivities (56–97%).



Scheme 244 Dinuclear zinc complex catalyzing the asymmetric Friedel–Crafts alkylation of unprotected pyrroles to nitroalkenes.

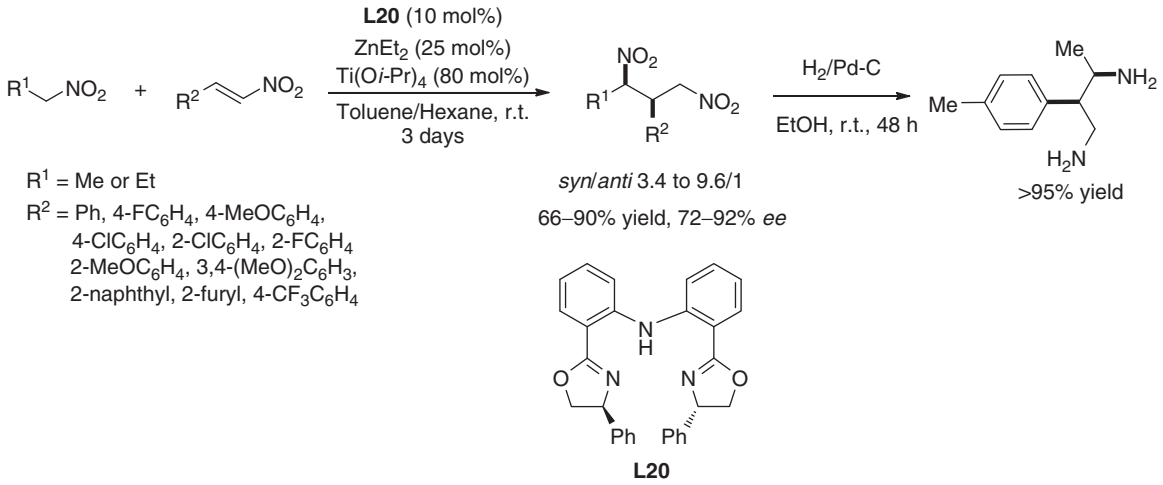
In 2010, the use of readily available chiral Schiff-base ligand **L19** in combination with $Zn(OTf)_2$ for the enantioselective Friedel–Crafts reaction of indoles with nitroalkenes was reported by Wang and coworkers (Scheme 245).[519] Various aromatic nitroolefins with different substituents on the aromatic ring were examined, leading to optically active Michael adducts in excellent yields and enantioselectivities (typically >90% *ee*).



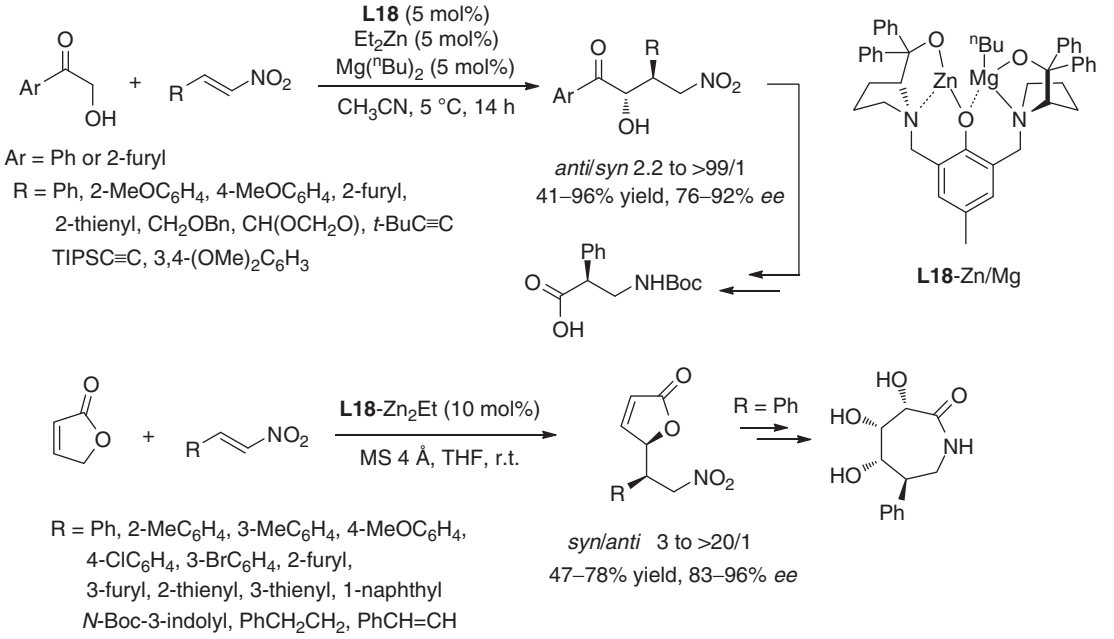
Scheme 245 Asymmetric Friedel–Crafts alkylation of indoles to nitroalkenes promoted by a Zn–Schiff base complex.

Nitoolefin Michael acceptors were also studied in ACA involving exotic C-nucleophiles such as nitroalkanes, *α*-hydroxyketones, or butenolides. In 2006, Du and coworkers demonstrated the efficiency of their bifunctional tridentate bisoxazoline ligand type for the $ZnEt_2$-mediated conjugate addition of nitromethane to *β*-nitrostyrene in the presence of $Ti(Oi\text{-}Pr)_4$.[520] Highest diastereo- and enantioselectivities (*syn*/*anti*: 6/1; 91% *ee*) were reached with tridentate bisoxazoline **L20** (Scheme 246). The scope was then extended to various nitroolefins and nitroalkanes with relatively good yields (66–90%) and high selectivities (up to 9,6/1 *syn*/*anti* ratio and 92% *ee*), except for the Michael donnor 2-nitropropane, which remained completely unreactive. Advantageously, the synthesized enantioenriched 1,3-dinitroalkanes could be further transformed into high useful chiral 1,3-diamines.

In the meantime, Trost and Hisaindee investigated the efficiency of their chiral dinuclear **L18** in the enantioselective addition of *α*-hydroxyketones to *β*-substituted nitroalkenes.[521] To this end, several homo- and hetero-dinuclear Zn and Mg complexes were evaluated. As depicted in Scheme 246, the highest stereocontrol was obtained with a Zn/Mg dinuclear catalyst, affording various 1,4-adducts in moderate to good yields (41–97%) with a *syn*/*anti* ratio ranging from 2.4/1 to >99/1 and excellent enantioselectivities (up to 92%). Interestingly, this methodology was applied to the synthesis of optically active *β*-amino acids. In 2009, the same group showed that the homo-dinuclear **L18**-Zn_2Et was effective for the vinylogous asymmetric Michael addition of butenolide to various aliphatic and aromatic nitroolefins (Scheme 247).[522] The resulting 1,4-adducts were isolated in good yields (47–78%) with excellent stereoselectivies (up to >20/1 *dr* and 96% *ee*). Additionally, these vinylogous Michael adducts could be converted in a straightforward manner into valuable enantioenriched chiral building blocks such as cyclic lactams.



Scheme 246 Asymmetric additions of nitroalkanes to nitroolefins catalyzed by a chiral Zn–bisoxazoline complex: direct access to optically active 1,3-diamines.

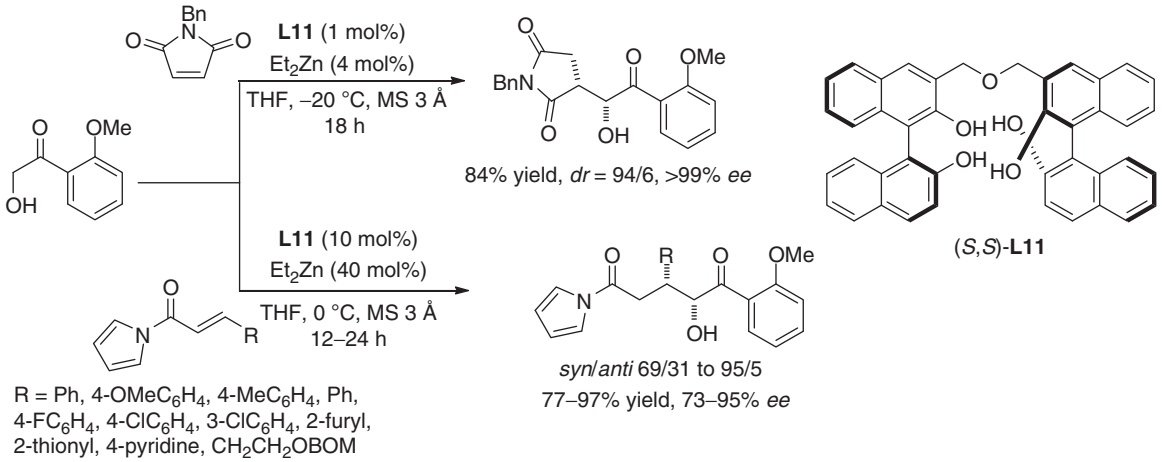


Scheme 247 Hetero- and homo-dinuclear catalysts for ACA of α-hydroxyketones and butenolide to nitroalkanes.

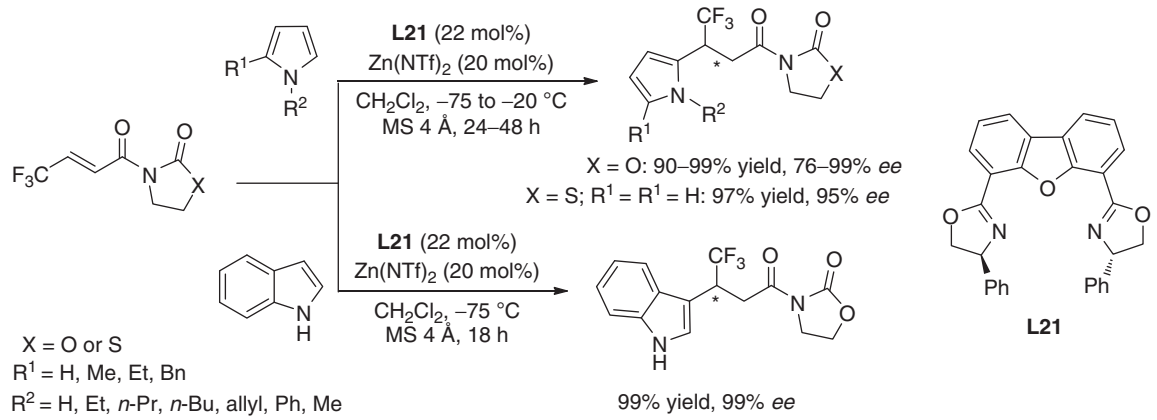
4.04.8.2.1.3 ACA of α,β-unsaturated amides, esters, and nitriles

Shibasaki and coworkers were the first to report a Zn-mediated asymmetric catalytic conjugate addition of C-nucleophiles to α,β-unsaturated amide. Based on their previous results obtained in ACA of α-hydroxyketones to enones involving the bimetallic Zn–Zn-linked BINOL complex **L11**-Zn_2 catalytic system, they decided to extend the methodology to *N*-benzylmaleimide[509] and α,β-unsaturated *N*-acylpyrroles[523] as Michael acceptors (Scheme 248). Remarkably, in the case of the maleimide substrate, the reaction required only 1 mol% of **L11** and 4 mol% of Et_2Zn to afford the 1,4-adduct in 84% yield, >99% *ee*, and in high *dr* (96/4 *syn*). With pyrrole derivatives, the corresponding Michael adducts were isolated in 77–97% yield with excellent *ee*s (up to 95%) and diastereomeric ratio ranging from 69/31 to 95/5 in favor of the *syn*-product.

Recently, the group of Shibata disclosed the first asymmetric Zn-mediated Friedel–Crafts akylation of pyrroles performed on acrylates (Scheme 249).[524] Catalyzed by $Zn(NTf)_2$ salt in the presence of chiral bisoxazoline ligand **L21**, various types of enantioenriched trifluoromethylated Michael adducts were produced in excellent yields (90–99%) with high *ee*s (up to 99%). The indole derivatives were also examined giving similar high yield and *ee*s (99%). This methodology was successfully applied to the synthesis of optically active trifluoronated heliotridanes. Later, α,β-unsaturated thiazolidinone was evaluated with pyrrole nucleophile, affording the desired adduct in 97% yield and 95% *ee*.[525]



Scheme 248 Asymmetric Michael addition of 2-hydroxyketone to *N*-benzylmaleimide and α,β-unsaturated *N*-acylpyrroles catalyzed by a Et_2Zn-linked BINOL complex.



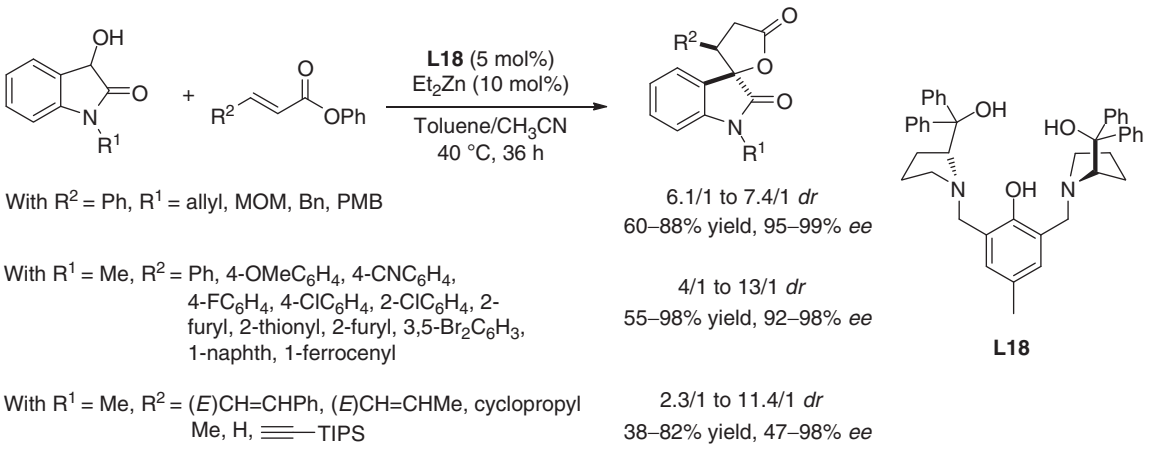
Scheme 249 Asymmetric Zn-catalyzed Friedel–Crafts akylation of pyrroles and indoles to acrylates.

Regarding α,β-unsaturated ester and nitrile Michael acceptors for Zn-catalyzed ECA, only few examples were described in the literature. In 2012, Trost and Hirano developed an asymmetric tandem Michael addition-transesterification of 3-hydroxyoxindoles to β-substituted enoates catalyzed by the dinuclear Zn-**L18** complex. This process was considered as an alternative and efficient synthetic route to the formation of highly desirable optically active spirocyclic δ-lactones (Scheme 250).[526] After a screening of several cinnamoyl acidic derivatives (pyrrole and indoles), the phenylester-based Michael acceptor appeared the most suitable candidate, affording exclusively the desired spiro-adduct in 89% yield with the highest diastereo- and enantioselectivity (9.2/1 *dr* and 96% *ee*). The scope was then extended to various β-substituted α,β-unsaturated phenylesters and 3-hydroxyoxindoles. Modest to excellent yields (38–98%), diastereoinduction up to 13/1 and enantiomeric excesses ranging from 47% to 99% were obtained. Remarkably, in the case of dienoates, 1,4-adducts were exclusively formed with excellent *ee*s (97–98%).

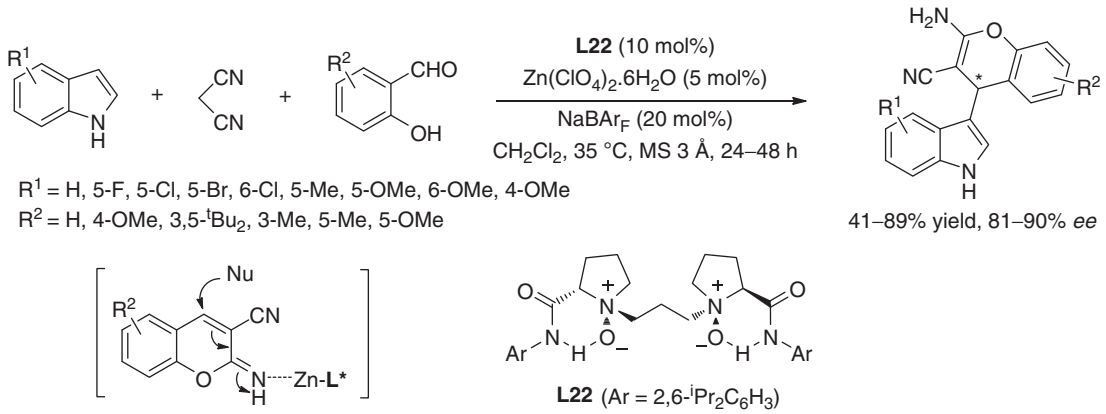
In the case of nitrile Michael acceptors, to the best of our knowledge, only one example was recently disclosed by Feng and coworkers in 2011, which was applied for the synthesis of optically active 2-amino-4H-chromene derivatives.[527] The catalytic asymmetric process involved a Friedel–Crafts alkylation of indole to an *in situ*-formed α,β-unsaturated nitrile resulting from a Knoevenagel/Pinner cyclization between salicyladehyde and malonitrile (Scheme 251). Catalyzed by $Zn(ClO_4)_2$ salt in the presence of bis-proline *N*-oxide ligand **L22,** various chromene products were isolated in modest to high yields (41–89%) and good enantioselectivities (up to 90%).

4.04.8.2.2 Addition of hetero-nucleophiles

To date, only two examples were reported concerning the ECA of hetero-nucleophiles catalyzed by Zn-based complexes. The first attempt was disclosed by Kanemasa and coworkers in 2002 with the addition of aldoximes to 3-crotonoyl-2-oxazolidinone and 1-crotonoyl-3-phenyl-2-imidazolidinone in the presence of catalytic amount of zinc(II)-perchlorate (Scheme 252).[528] Despite a screening of various chiral ligands, the resulting *N*-alkylated nitrones were isolated in good yields (up to 94%) but the

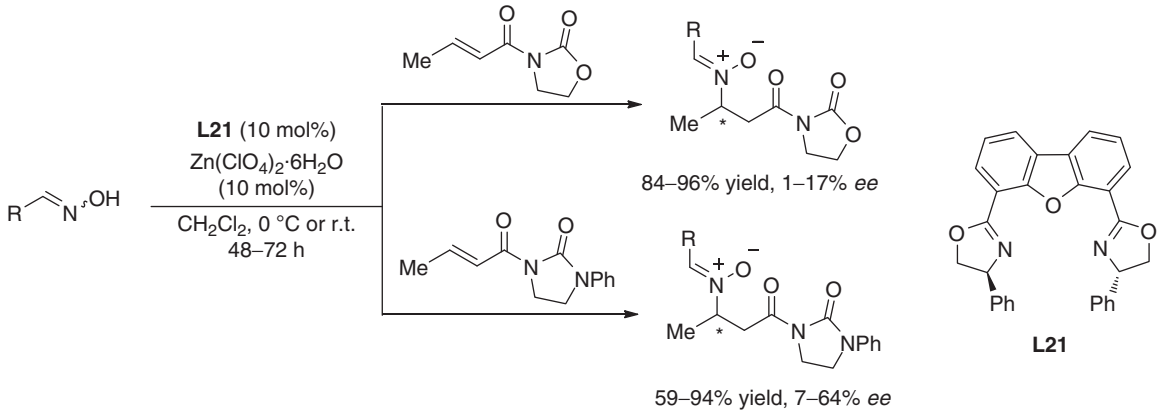


Scheme 250 Asymmetric Zn-catalyzed tandem Michael addition-transesterification of 3-hydroxy oxindoles to β-substituted enoates: synthesis of spirocyclic δ-lactones.



Scheme 251 Enantioselective one-pot synthesis of 2-amino-4H-chromenes catalyzed by an *N,N'*-dioxide Zn(II) complex.

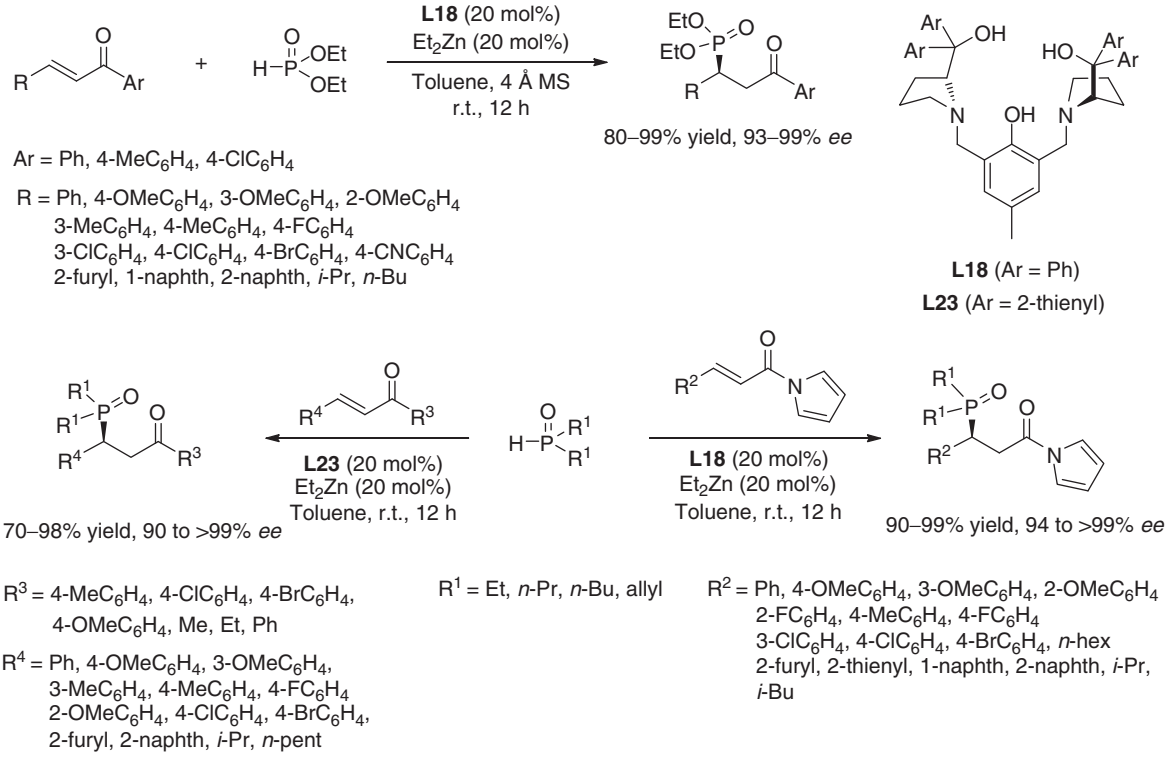
enantioselectivities remained extremely low to moderate (1–64%). The highest selectivity of 64% of *ee* was reached with the α,β-unsaturated imidazolidinone Michael acceptor in the presence of bisoxazoline ligand **L21**.



Scheme 252 First example of enantioselective conjugate addition of hetero-nucleophile (aldoxime) promoted by Zn(II) complexes.

Seminal works in the area of catalytic asymmetric 1,4-conjugate hydrophosphinylation of various Michael acceptors were achieved by Wang and coworkers since 2009. Using the Trost's dinuclear Zn-based catalytic system (Zn-**L18** complex), they developed an efficient process to afford a wide range of optically active 1,4-hydrophosphinylated adducts with remarkable

selectivities (Scheme 253). Aromatic enones and diethylphosphites were first studied,[529] leading to the corresponding Michael adducts in high yields (80–99%) and excellent enantioselectivities (93–99%). This methodology was then successfully extended to dialkylphosphine oxides and *N*-acylpyrroles.[530] Yields of 99% and above and enantioselectivities ranging from 94% to 99% were obtained, allowing producing in a straightforward synthetic route highly desirable chiral phosphine oxides and phosphines. Through a structural modification of the Trost's ligand, the phospha-Michael reaction was then applied to *β*-substituted aromatic and aliphatic enones. Catalyzed by the newly developed dinuclear Zn-**L23** complex, various 1,4-adducts were obtained with similar high yield and *ee*s (90% to >99% *ee*).[531]



Scheme 253 Asymmetric 1,4-conjugate hydrophosphinylation of *α,β*-unsaturated enones and *N*-acylpyrroles promoted by chiral dinuclear Zn(II) complexes.

4.04.9 Ca/Sr/Ba Metal-Catalyzed Enantioselective Conjugate Addition

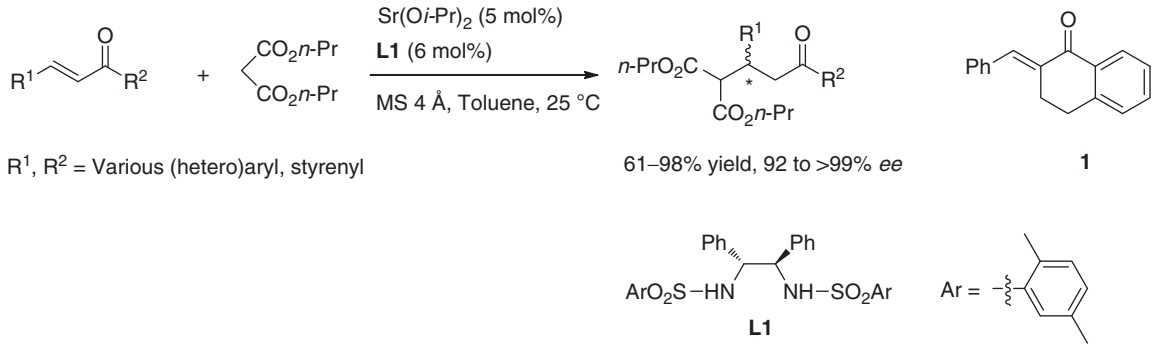
Alkaline earth metals appear as particularly attractive for the development of metal-catalyzed transformations. First, they are abundant, cheap, and are suitable for more environmentally friendly chemistry; particularly, calcium which is nontoxic. Second, alkaline earth metal-based species exhibit both significant Brønsted basicity and Lewis acidity.[532] Nevertheless, the behavior of chiral complexes derived from Ca, Ba, and Sr in ECA has been not much explored. However, efficient catalytic systems for the formation of C–C bonds have been reported in recent years.

4.04.9.1 *α,β*-Unsaturated Enones

4.04.9.1.1 Addition of β-dicarbonyl-type nucleophiles

The first report, dated 2001, of a Ca-catalyzed enantioselective 1,4-addition described the reaction of malonates to (a)cylic enones. Using 15 mol% of a BINOL/Ca catalyst, the adducts were obtained in good yields but the enantioselectivities, contained between 21% and 88%, were strongly dependent on the nature of both the malonate and the enone.[533] The same group reported in 2005 the enantioselective Michael addition of cyclic *β*-ketoesters to MVK using 10 mol% of H_8-BINOL/Ca-based catalyst. The products, which contain chiral quaternary centers, were obtained with *ee*s up to 80%.[534] The use of a supported chiral-Ca catalyst in Michael addition was also examined by the same group, but moderate *ee*s were reached.[535]

A very efficient catalytic system was reported by Kobayashi in 2008 for the Michael addition of malonates on chalcones (Scheme 254).[536]

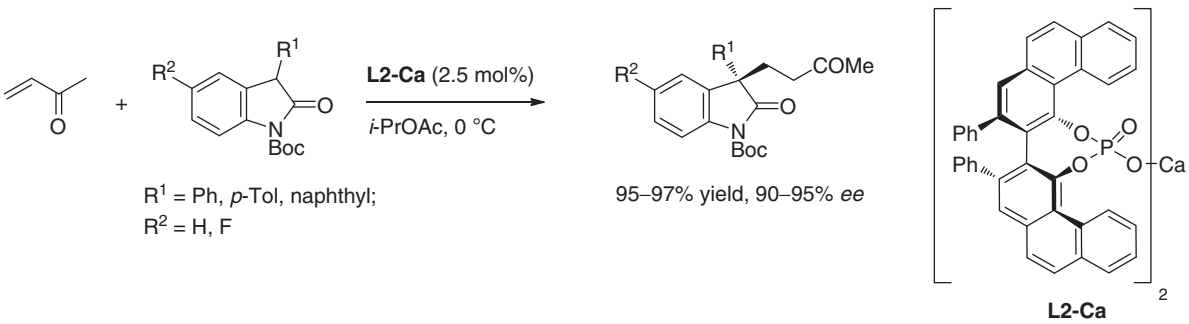


Scheme 254 Enantioselective Sr/**L1**-catalyzed 1,4-addition of malonates to chalcones.

Using a Sr(O*i*-Pr)$_2$/bis-sulfonamide **L1** catalytic system, excellent *ee*s (up to >99%) were reached in the addition of *n*-propyl malonate to a series (20 examples) of acyclic (hetero)aromatic enones, including a dienic enone. Interestingly, Ca and Ba-based catalysts were also tested but led to worse results. Besides, it is worth noting that when the catalyst loading was diminished from 5 mol% to 0.5 mol%, this did not lead to any significant drop in enantioselectivity. The same group showed that the use of Sr(HMDS)$_2$ as the metal source allowed to improve slightly the *ee*s and the yields in most cases.[537] Using this metal source, the reaction could also be successfully (50% yield, 94% *ee*) extended to cyclic chalcone **1** (Scheme 254).

4.04.9.1.2 Addition of oxindoles

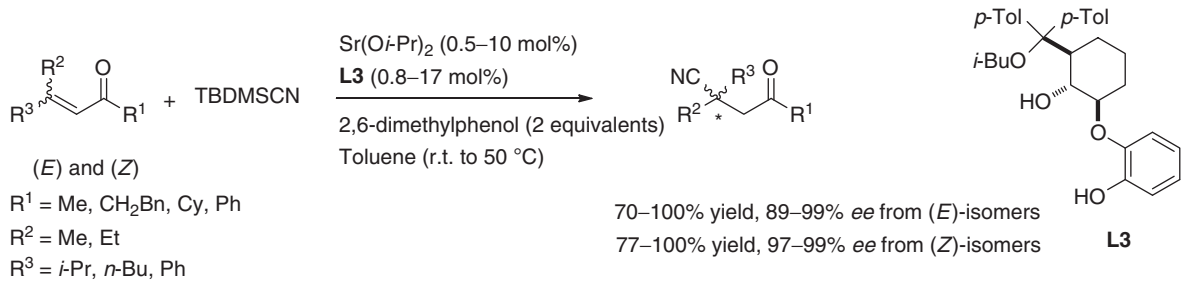
The enantioselective-catalyzed conjugate addition of four different oxindoles to MVK using 2.5 mol% of **L2-Ca** as the catalyst was reported in 2011 (Scheme 255). The products, which exhibit a chiral quaternary carbon center, were produced in high yields and *ee*s (respectively up to 97% and 95%).[538]



Scheme 255 Enantioselective **L2-Ca**-catalyzed conjugate addition of oxindoles to MVK.

4.04.9.1.3 Addition of cyanide

The use of cyanide ion as nucleophile in the conjugate addition to β,β-disubstituted acyclic enones was investigated by Shibasaki (Scheme 256).[539]

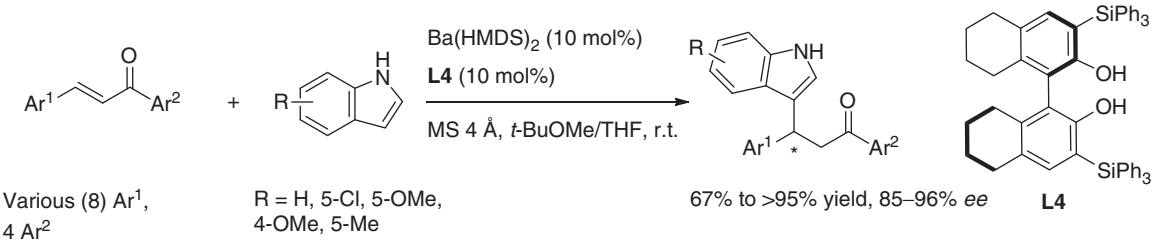


Scheme 256 Enantioselective Sr/**L3**-catalyzed 1,4-addition of cyanide ion on β,β-disubstituted acyclic enones.

Using a Sr(O*i*-Pr)$_2$/**L3** catalyst and TBDMSCN as the cyanide source, the chiral quaternary centers were formed in good to very high *ee*s (up to 99%). In most cases, both (*E*) and (*Z*) isomers were tested and gave opposite enantiomers. The behavior of one *α*,*β*, *β*-trisubstituted enone was also examined under the same reaction conditions and it proved to be a valuable substrate.

4.04.9.1.4 Addition of indole (Friedel–Crafts reaction)

Kobayashi explored the Friedel–Crafts reaction between indoles and a wide range of chalcones bearing EDG or EWG substituents at different positions of the *β*-aryl group.[540] Using a Ba(HMDS)$_2$/**L4** catalyst, which acts as a chiral Bronsted base catalyst in the reaction, the adducts were isolated in most cases in high *ee*s (up to 96%) and good to excellent yields (Scheme 257).

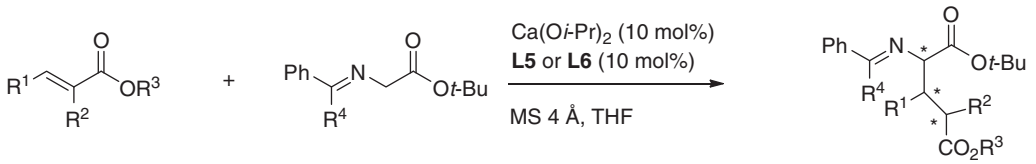


Scheme 257 Enantioselective Ba/**L4**-catalyzed 1,4-addition of indoles to enones.

However, a lower *ee* (70%) was observed when 2-methylindole was considered. A noteworthy influence of the solvent on the outcome of the reaction was also observed.

4.04.9.2 Unsaturated Esters

Kobayashi studied the conjugate addition of different types of amino acid derivatives on unsaturated esters. The reaction between glycine Schiff base **3** (Scheme 258; R^4 = Ph) and *α*-substituted *α*,*β*-unsaturated esters **2** was first reported.[541] Using 10 mol% of a Ca/bisoxazoline **L5** catalyst, the products were formed in good to high *ee*s (up to 99%), but low to good *dr* which were strongly dependent on the nature of the substituent on the *α*-position (R^2) of the double bond.



2 : R^1 = H
R^2 = H, Me, Et, *i*-Pr, *i*-Bu, Ph, Cl
R^3 = Me, Et, *t*-Bu

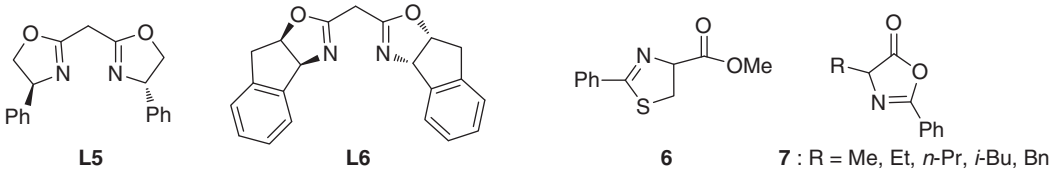
3 : R^4 = Ph

56% to >95% yield, 80–99% *ee*, 55/45 to 91/9 *dr*

4 : R^1 = Me, Et, *n*-Bu, *i*-Bu, CH$_2$OBn
R^2 = H;
R^3 = Me, Et

5 : R^4 = *t*-Bu

56–97% yield, 82–99% *ee*, up to >99/1 *dr*



Scheme 258 Enantioselective Ca-catalyzed conjugate additions of glycine Schiff base to unsaturated esters.

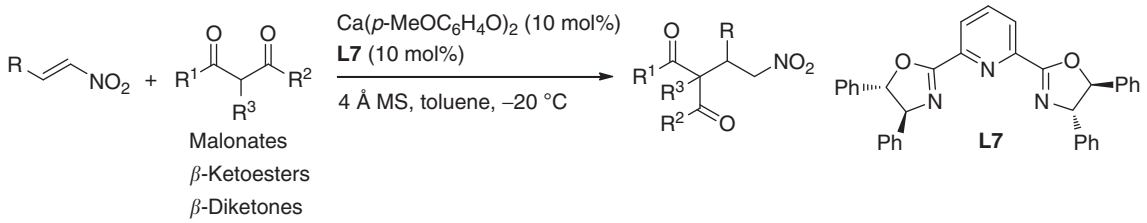
When methyl crotonate was used as the acceptor, the formation of the Michael adduct was not observed. Instead, a product arising from [3+2] cycloaddition was obtained. However, when one Ph group in the imino function was changed to a *t*-Bu (**5**, R^4 = *t*-Bu), it became possible to perform the conjugate addition on crotonates and other *β*-substituted *α*,*β*-unsaturated esters **4** (Scheme 258). In the presence of 10 mol% of a Ca/bisoxazoline **L6** catalytic system, the reaction gave usually the Michael adducts in excellent enantioselectivities and diastereomeric ratios.[541b,542] These compounds can further be efficiently converted into 3-alkyl glutamic acids. Moreover, mechanistic studies were undertaken.[541b]

The enantioselective 1,4-addition of cysteine derivative **6** (see Scheme 258) on methyl acrylate was also examined using Ca/**L5** catalytic system. The quaternary stereocenter product was isolated in good *ee* (86%).[541b]

Azlactones **7** (Scheme 258) were also considered as nucleophilic partners toward various acrylates using a Ca(O*i*-Pr)$_2$/pyridinebisoxazoline catalytic system. The products, which are precursors of α-alkyl glutamic acids, were formed in enantioselectivities of varying values, ranging from 64% to 84%.[543]

4.04.9.3 Nitroolefins

A Ca/Pybox catalytic system was evaluated in the 1,4-addition of various 1,3-dicarbonyl compounds to a series of nitroalkenes which, for the most part, bore an aryl group in the β-position (Scheme 259 and Table 7, entry 1).[544] With regard to malonates, the *ee*s were usually excellent when methyl (or ethyl) malonate was reacted with (hetero)aryl nitroolefins (92–96%), whereas they were slightly lower (87%) when the reaction was run with 2-nitrovinylcyclohexane (R=Cy) or α-substituted malonates ($R^3 \neq H$) and moderate (65%) when the β-carbon within the nitroalkene held an *ortho*-tolyl group (R=*o*-Tol). β-Ketoesters furnished the expected adducts in high yields and *ee*s but low to moderate (at most 76/24) diastereoisomeric ratios (entry 2). A less satisfactory result was noted when acetylacetone was engaged in the reaction (entry 3).



Scheme 259 Enantioselective Ca-catalyzed 1,4-addition of β-dicarbonyl compounds to nitroalkenes.

Table 7 Enantioselective Ca-catalyzed 1,4-addition of β-dicarbonyl compounds to nitroalkenes

Entry	*R*	*R^1, R^2*	*R^3*	*Yield (%)*	ee *(%)*
1	(Hetero)Ar, Cy	$R^1=R^2=$OMe, OEt	H, Me, OMe	73 to >95	65–96
2	Ph	$R^1=$OMe, O*t*-Bu; $R^2=$Me	H	90–91	90–93
3	Ph	$R^1=R^2=$Me	H	54	78

4.04.9.4 Unsaturated Amides

4.04.9.4.1 Addition of amino acid derivatives to α,β-unsaturated Weinreb amides

The enantioselective 1,4-addition of glycine Schiff bases **3** and **5** to α,β-unsaturated Weinreb amides was examined under the conditions which were used for their addition to unsaturated esters (see Section 4.04.9.2).[541,542] The most impressive results were obtained for the reaction of **5** with β-substituted Michael acceptors **9**. Indeed, both high yields (up to 94%) and *ee*s (up to 98%) were reached in the three examples reported (Scheme 260).

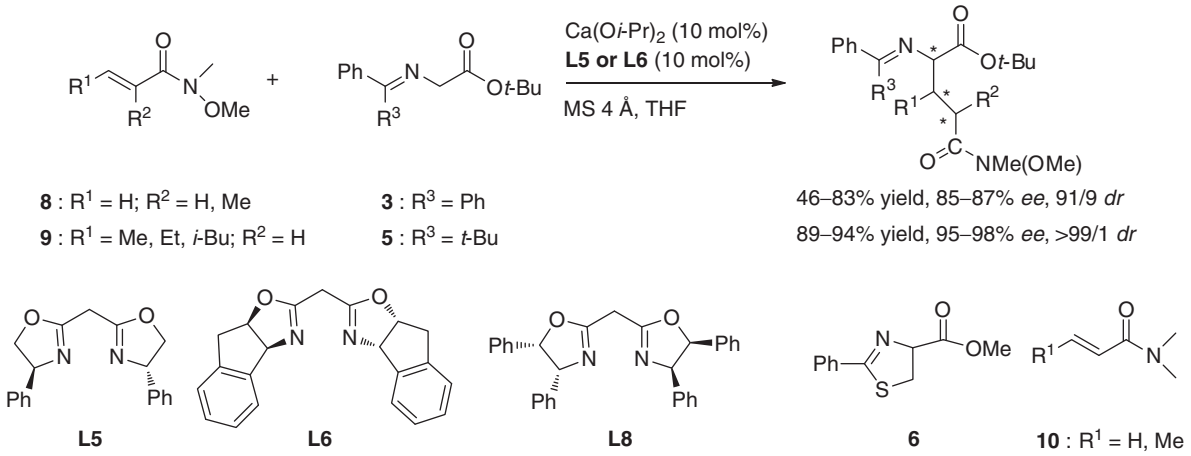
The behavior of Cys derivative **6** (see Scheme 260) toward Weinreb amide of acrylic acid was also examined using the Ca(O*i*-Pr)$_2$/**L8** (see Scheme 260) catalytic system.[541b] The quaternary chiral center product was isolated in good yield but in less remarkable *ee* (80%).

Besides, the addition of glycine Schiff base derivative **5** to *N*,*N*-dimethyl amides counterparts **10** (see Scheme 260) was also considered by the same authors.[541b] However, a dramatic drop in the isolated yields (at best 22%) was noted, compared to that obtained with Weinreb amide analogs.

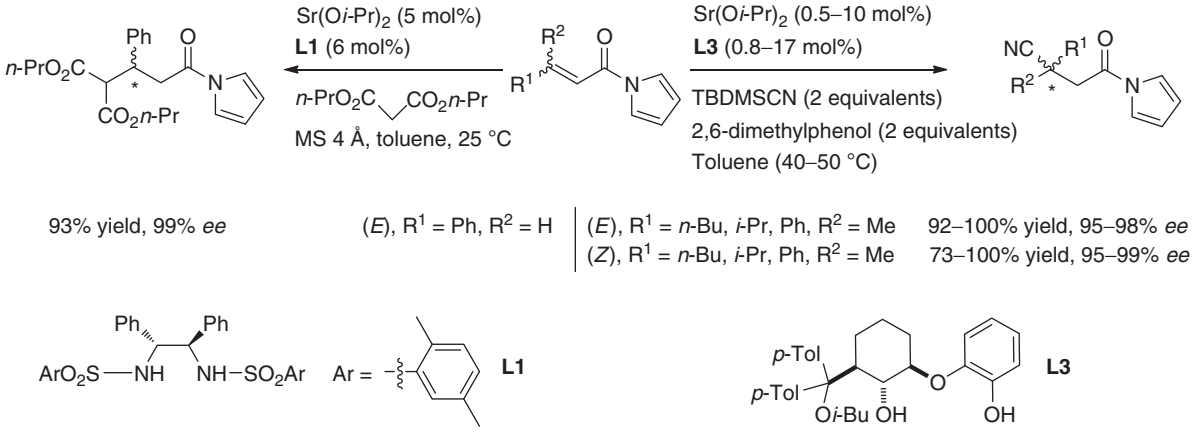
4.04.9.4.2 Addition to α,β-unsaturated N-acylpyrroles

Among the numerous examples of Michael acceptors that were reacted with *n*-propyl malonate in the presence of Sr(O*i*-Pr)$_2$/**L1** as the catalyst (see Section 4.04.9.1.1), the case of *N*-acylpyrrole derived from cinnamic acid was examined (Scheme 261).[536] The catalytic system proved to be efficient with this substrate as well, as remarkable yield (93%) and enantioselectivity (99%) were reached.

The conditions used for the conjugate addition of cyanide to enones (see Section 4.04.9.1.3) were also tolerant of β,β-disubstituted α,β-unsaturated *N*-acylpyrroles (Scheme 261).[539] Using 0.5–10 mol% of Sr(O*i*-Pr)$_2$ and 0.8–17 mol% of the chiral ligand **L3**, both (*Z*) and (*E*) isomers of the substrate gave the expected quaternary stereocenter products in high *ee*s (up to 99%).



Scheme 260 Enantioselective Ca-catalyzed 1,4-addition of glycine Schiff bases to α,β-unsaturated Weinreb amides.



Scheme 261 Enantioselective Sr-catalyzed 1,4-additions to α,β-unsaturated *N*-acylpyrroles.

4.04.9.5 Miscellaneous Michael Acceptors

An enal[533] and one α,β-unsaturated sulfone[541b] were also evaluated as Michael acceptors in enantioselective Ca-catalyzed 1,4-additions. They were reacted respectively with *i*-propyl malonate and a glycine Schiff base. In both cases, the products were formed in moderate *ee*s.

4.04.10 Alkali Metal-Catalyzed Enantioselective Conjugate Addition

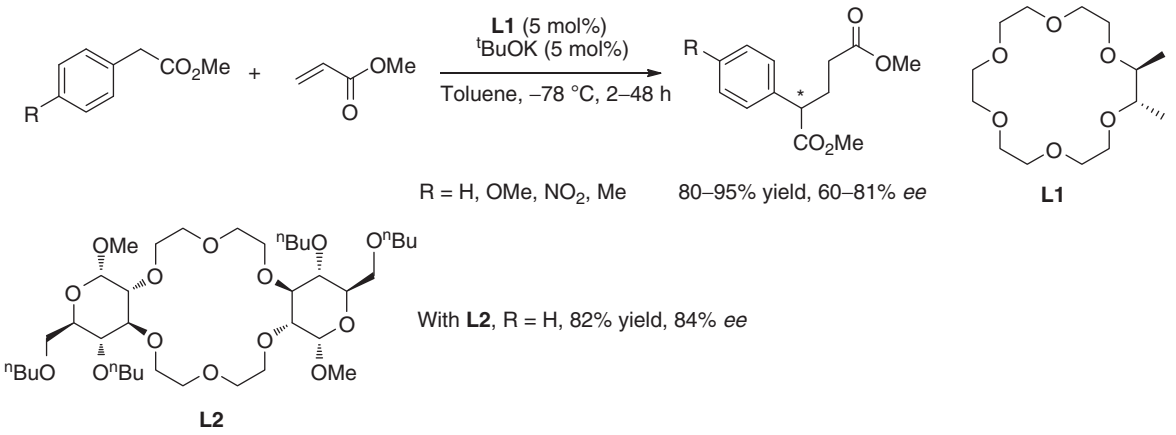
4.04.10.1 ACA of α,β-Unsaturated Esters

4.04.10.1.1 Addition of acetate nucleophiles

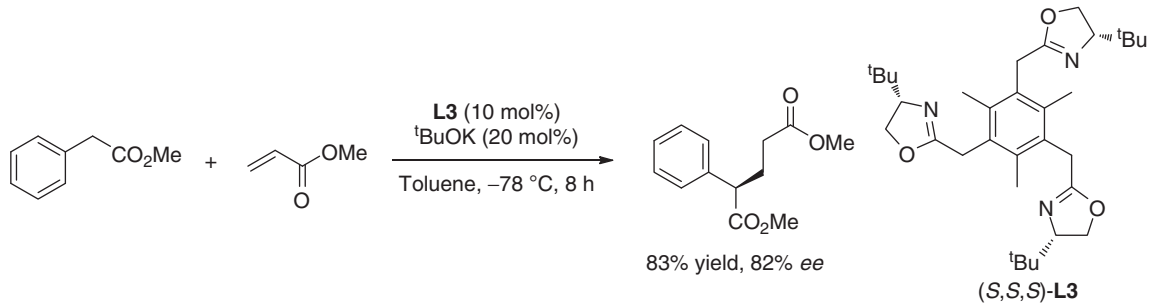
The first ECA catalyzed by chiral alkali-based complexes was disclosed by Koga and coworkers in 1989. In this pioneering study, a wide range of optically active crown ether ligands in association with potassium *ter*-butoxide was screened for the Michael addition of phenylacetate derivatives to methyl acrylate (Scheme 262).[545] The best results were reached with crown ether **L1**, which afforded the resulting 1,4-adducts in good to excellent yields (80–95%) with high enantioselectivities (up to 81%)

Six years later, Toke et al. examined the efficiency of several chiral crown ethers anellated to sugar units for the addition of methyl phenyl acetate to methyl acrylate (Scheme 262).[546] The crown ether **L2** was the highest selective ligand, leading to the Michael product in 82% of yield and 84% *ee*. Molecular modeling was further investigated to explain the stereochemical outcome of the enantioselective addition.[547]

In 2001, Ahn and Kim developed a novel tripodal oxazoline-based ligand **L3**, promoting in the presence of potassium *ter*-butoxide, the enantioselective addition of methyl phenyl acetate to methyl acrylate (Scheme 263).[548] After an optimization of reaction conditions, up to 83% of yield and 82% of *ee* were obtained.



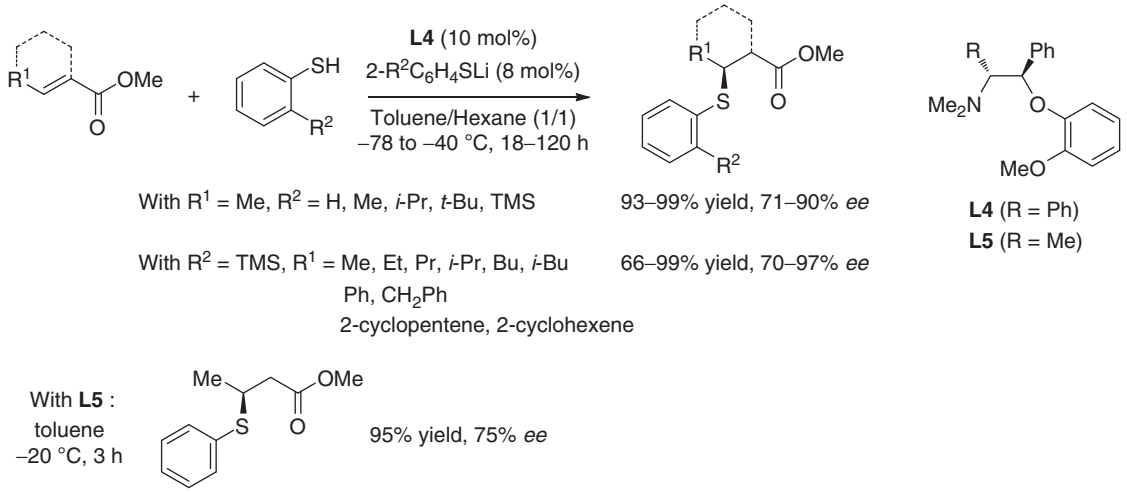
Scheme 262 Chiral potassium crown ethers used to catalyze the asymmetric Michael addition of phenylacetate derivatives to methyl acrylate.



Scheme 263 Asymmetric Michael addition of phenylacetate derivatives to methyl acrylate catalyzed by tripodale oxazoline–potassium complexes.

4.04.10.1.2 Addition of hetero-nucleophiles

The first example of asymmetric Michael addition of hetero-nucleophiles to electron-deficient olefins catalyzed by alkali-based complexes was disclosed by Tomioka and coworkers in 1997.[549] In this seminal report, they described that a combination of lithium thiophenolate and an external tridentate amino ether ligand **L4** promoted efficiently the asymmetric Michael reaction of thiophenols and methyl crotonate to form sulfur–carbon bonds (Scheme 264). After a screening of several thiols, the highest enantioselectivity (90% *ee*) was reached with 2-(trimethylsilyl)thiophenol. The scope was then successfully extended to various α, β-unsaturated esters and 2-(trimethylsilyl)thiophenol as nucleophile. Remarkably, all corresponding thio-alkylated 1,4-adducts were obtained in high yields (66–99%) and excellent *ee*s (up to 97% *ee*).



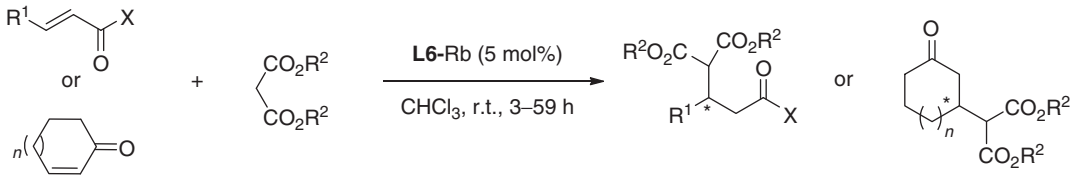
Scheme 264 First asymmetric Michael addition of thiophenols to various α,β-unsaturated esters catalyzed by chiral lithium complexes.

Further structural modifications of amino ether ligands were proposed by Tomioka et al. to improve the enantio-induction of the addition of the thiophenol to methyl crotonate.[550] Among all bidentate and tridentate ligands studied, **L5** was the most efficient, affording the 1,4-adduct in 95% of yield with 75% *ee* (Scheme 264).

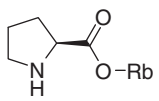
4.04.10.2 ACA of α,β-Unsaturated Enones and Enals

4.04.10.2.1 Addition of malonate nucleophiles

The asymmetric alkali-catalyzed Michael addition of malonates to α,β-unsaturated carbonyl derivatives has been intensively studied since the last two decades. The first attempt was by Yamagushi et al. in 1991 during the addition of dimethylmalonate to various enals catalyzed by 10 mol% of (*L*)-proline lithium salt.[551] Unfortunately, no asymmetric induction was observed despite the use of the enantiopure amino acid. Two years later, the same group proposed to replace the alkali source by rubidinium (Scheme 265).[552] With this new (*L*)-proline **L6**-Rb salt, enantioselectivities were finally observed for the addition of diisopropyl malonate to various enal and enone Michael acceptors (up to 77% *ee*). Of note, acyclic ketones appeared more suitable for this transformation than cyclic as well as enal substrates. In 1996, the authors studied the effect of the ester group of malonate on the enantio-induction of the addition. Interestingly, enhanced selectivities were attained with *t*-Bu ester for various acyclic and cyclic enones, including notably macrocyclic enones (from 65% to 86% *ee*).[553]



For R^2 = *i*-Pr
- X = Me, *n*-Pr R^1 = Me, *n*-Pent, Ph 62–79% yield, 53–77% *ee*
- X = H R^1 = Me or *n*-Pr 58–63% yield, 35–41% *ee*
- 2-Cycloheptenone 91% yield, 59% *ee*
- 2-Cyclohexenone 87% yield, 49% *ee*

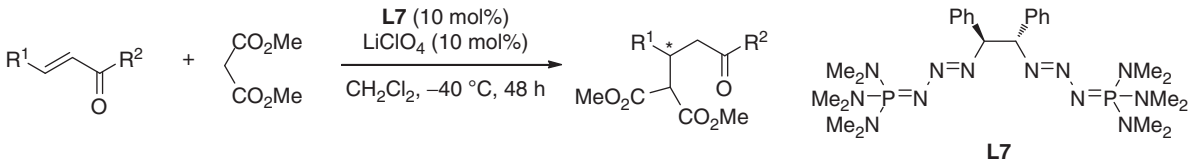


L6-Rb

For R^2 = *t*-Bu
- X = Me R^1 = Me, *n*-Pent, Ph, CH_2CH_2Ph 62–79% yield, 53–77% *ee*
- 2-Cycloheptenone 84% yield, 65% *ee*
- 2-Cyclohexenone 75% yield, 74% *ee*
- (*E*)-2-Cyclodecenone 45% yield, 81% *ee*
- (*E*)-2-Cyclopentadecenone 54% yield, 82% *ee*

Scheme 265 First asymmetric Michael addition of malonates to various α,β-unsaturated enals and enones catalyzed by a chiral (L)-proline-rubidinium salts.

In 2008, Naka et al. developed a chiral bisphosphazide ligand **L7** affording, when complexed with perchlorate lithium salts, a dual basic enantioselective catalyst for the addition of malonate derivatives to various chalcones (Scheme 266).[554] Interestingly, high isolated yields (up to 99%) were observed with good enantio-induction levels (83–88% *ee*). However, no enantioselectivity was observed in the case of the bis-nitrile nucleophile.



L7

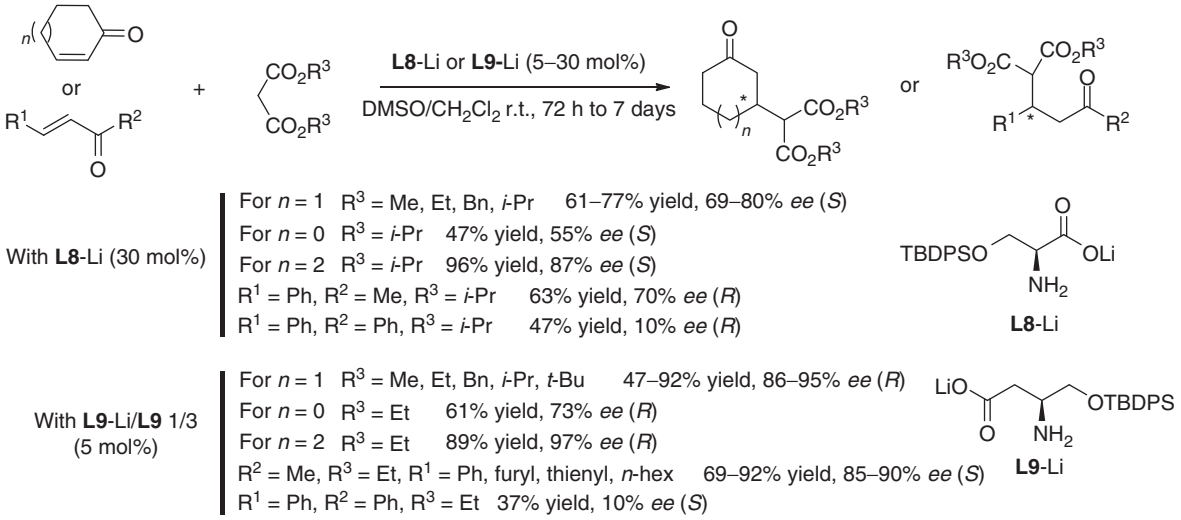
R^2 = Ph, R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 2-ClC_6H_4, 2-furyl, 2-pyridyl 41 to >99% yield, 84–88% *ee*

R^1 = Ph, R^2 = 4-ClC_6H_4 92% yield, 83% *ee*

Scheme 266 Asymmetric Michael addition of malonates to aromatic enones catalyzed by a chiral bisphosphazide-lithium salt.

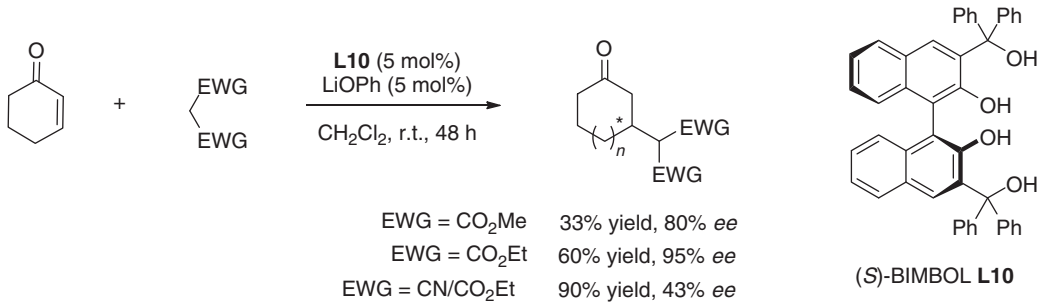
In the meantime, Yoshida et al. proposed to examine chiral primary amine ligands instead of secondary amines such as the previously reported (*L*)-proline.[555] To this end, several natural α-amino acids as well as their protected derivatives were screened for the addition of dimethylmalonate to 2-cyclohexenone (Scheme 267). The highest selectivity (69% *ee*) was reached with

TBDPS-O-protected (*L*)-serine **L8** at 30 mol% of loading. The methodology was then extended to various malonates and enone substrates, affording the expected 1,4-adducts in modest to good yields (47–96%) and high enantioselectivities (up to 87%), except for the chalcone (10% *ee*). Two years later, the same authors developed a new lithium-based catalyst derived from an optically active beta-amino acid **L9** (Scheme 267).[556] The enantioselectivies were significantly improved for various 1,5-ketoesters, reaching up to 97% *ee*. Unfortunately, the catalytic system was found to be inefficient toward chalcone substrates.



Scheme 267 Asymmetric Michael addition of malonates to various cyclic and acyclic enones catalyzed by chiral α- or β-amino acid lithium salts.

In 2011, Belokon et al. examined the potential of several chiral lithium salts derived from optically active binaphthols in the enantioselective addition of malonates to 2-cycohexenones (Scheme 268).[557] Up to 95% of enantioselectivity was reached with (*S*)-BIMBOL ligand **L10**. Nevertheless, in the case of the cyanophenylacetic ester nucleophile, the expected 1,4-adduct was formed in 90% of yield, but the selectivity dropped to 43% *ee*.

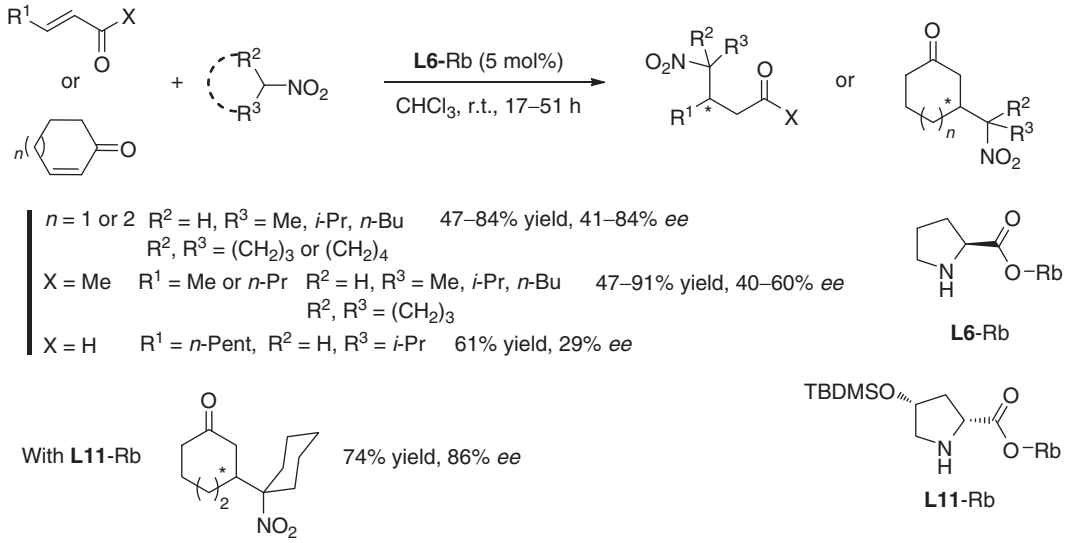


Scheme 268 Chiral lithium salts derived from optically active binaphthols in the enantioselective addition of malonates to 2-cycohexenones.

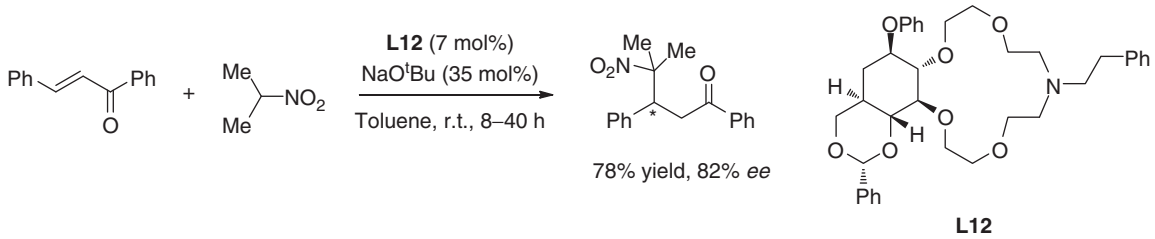
4.04.10.2.2 Addition of nitro-alkane nucleophiles

Nitro-alkanes represent interesting nucleophiles for C–C bond formation, as the nitro-group can be easily converted into various functionalities. This kind of C-nucleophiles was scarcely used for the alkali-catalyzed enantioselective Michael addition involving prochiral enones and enals. In 1994, Yamagushi et al. studied their previously developed (*L*)-proline rubidinium salt **L6**-Li for the asymmetric 1,4-addition of nitroalkanes to various cyclic and acyclic enones as well as enals.[558] The corresponding 1,4-adducts were isolated in modest to high yields (47–91%) with up to 84% of enantioselectivity (Scheme 269). Later, the same authors screened various cyclic amino acid Rb-salts to enhance the enantio-induction of the reaction. However, similar *ee*s were generally observed, showing the slight influence of the proline-substituent on the selectivity of the addition.[559] A maximum of 86% *ee* was reached with the (2*S*,4*R*)-4-(*t*-butyldimethylsilyloxy) prolinate **L11**-Rb for the addition of nitro-cyclohexyl to 2-cyclopentenone.

In 1998, Toke and coworkers developed various chiral azacrown ethers derived from D-glucose for the Michael addition of 2-nitropropane to chalcone.[560] In the presence of sodium *tert*-butoxide as base (35 mol%), the azacrown ether **L12** (7 mo%) was the most efficient ligand, affording the 1,4-adduct in 78% of yield and 82% *ee* (Scheme 270).



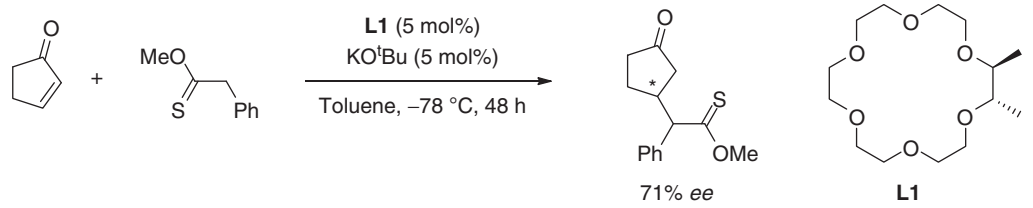
Scheme 269 Chiral proline-based rubidinium salts for the enantioselective Michael addition of nitro-alkanes to enones and enals.



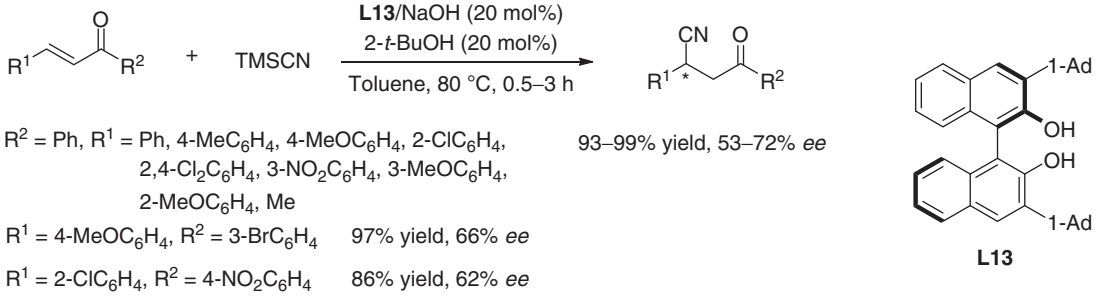
Scheme 270 Enantioselective Michael addition of 2-nitropropane to chalcone catalyzed by a chiral azacrown ether sodium salt.

4.04.10.2.3 Miscellaneous C-nucleophiles and hetero-nucleophiles

In 1992, Koga and coworkers proposed to extend the scope of their catalytic system involving optically active crown ether ligand **L1** and potassium *ter*-butoxide for the Michael addition of methyl phenylthioacetate to 2-cyclopentenone (Scheme 272).[561] The resulting 1,4-adduct was isolated with up to 71% of enantioselectivity (Scheme 271).



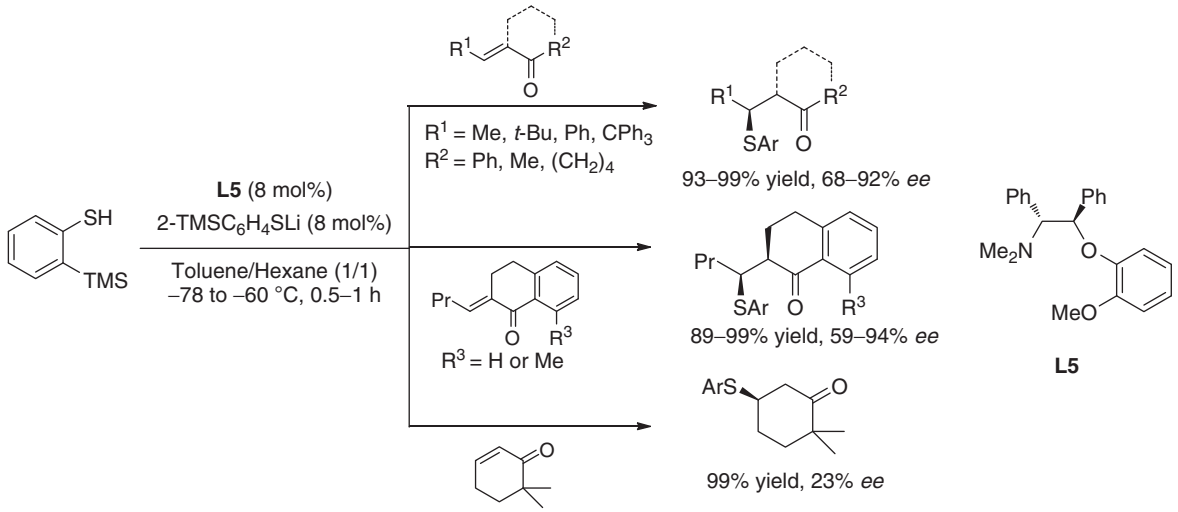
Scheme 271 Chiral potassium crown ethers used to catalyze the asymmetric Michael addition of methyl phenythioacetate to 2-cyclohexenone.



Scheme 272 Chiral sodium phosphate promoting the asymmetric Michael addition of TMSCN to aromatic enones.

To the best of our knowledge, only one example of enantioselective addition of the cyano group to α,β-unsaturated enones promoted by chiral alkali catalysts has been reported to date. In 2010, Chen and coworkers developed an efficient chiral sodium phosphate salt **L13** to catalyze the 1,4-addition of TMSCN to aromatic enones (Scheme 272).[562] Excellent yields (86–97%) were obtained for various Michael adducts with modest to good enantioselectivities (up to 71%).

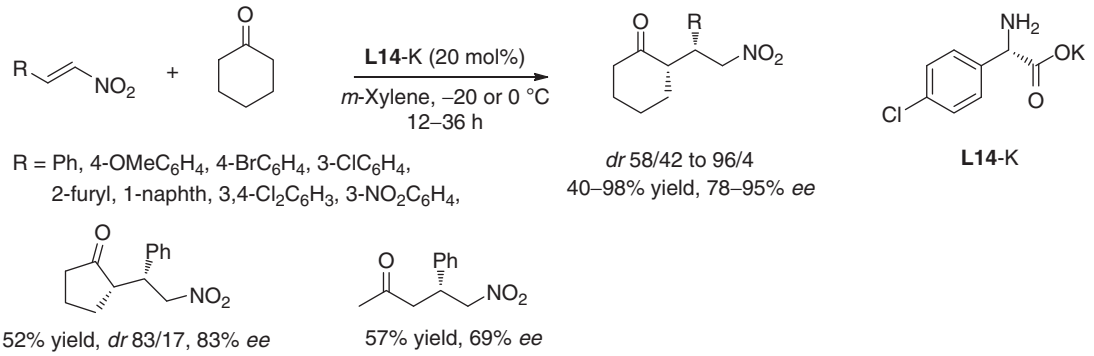
In 2002, Tomioka and Nishimura reported the unique example of asymmetric arylthiol Michael additions to α,β-unsaturated ketones catalyzed by the alkali-based complex **L5**-Li.[563] Various cyclic and acyclic enones were reacted with 2-(trimethylsilyl) thiophenol to afford corresponding thio-alkylated 1,4-adducts in high yields (89–99%) and excellent *ee*s (up to 94% *ee*), except for 6,6-dimethyl-2-cyclohexenone (23% *ee*) (Scheme 273).



Scheme 273 Asymmetric arylthiol Michael addition to various α,β-unsaturated enones catalyzed by a chiral lithium complex.

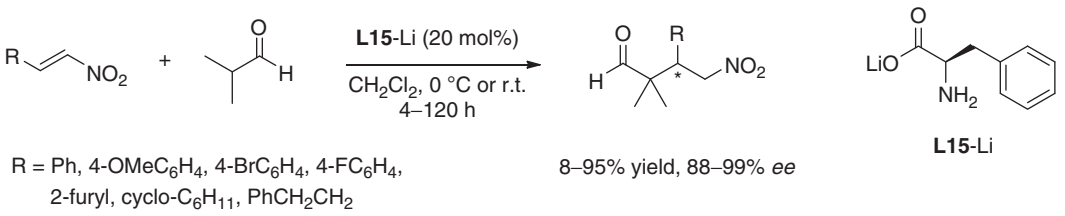
4.04.10.3 ACA of Nitroolefins

Nitroolefins were scarcely studied in alkali-promoted catalytic ECA of C-nucleophiles. The first example was disclosed by Feng and coworkers in early 2007.[564] They developed a catalytic system by treating several optically active α-amino acids with an equivalent of MOH (M = Li, Na, or K). The potassium salt of amino acid **L14** appeared the most efficient for the addition of cyclohexanone to β-nitro-styrene yielding the *syn* adduct with 84% *ee* (*syn*/*anti* ratio 76/24) (Scheme 274). Various nitroalkenes were then evaluated, leading to corresponding Michael adducts in moderate to high yields (40–98%), relatively good diastereoselectivities (up to 96/4), and high *ee*s (61–95%). Cyclopentanone and acetone were also examined, giving similar high selectivities.



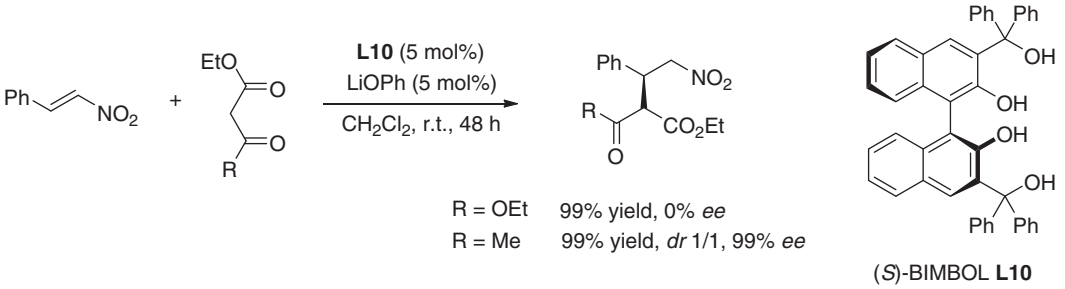
Scheme 274 Asymmetric Michael addition of ketones to nitroolefins catalyzed by a chiral potassium α-amino acid salt.

In 2008, Yoshida and coworkers reported the enantioselective addition of isobutyraldehyde to various nitroalkenes catalyzed by α-amino acid lithium salts.[565] Among all amino acids screened, (*L*)-phenylalanine **L15**-Li gave the highest selectivities, affording the desired quaternary carbon-containing nitroalkanes in low to good yields (8–92%) and high enantioselectivities (up to 99% *ee*) (Scheme 275).



Scheme 275 (L)-Phenylalanine lithium salt as catalyst for asymmetric Michael addition of isobutyraldehyde to nitroolefins.

In 2011, Belokon and coworkers evaluated the potential of (S)-BIMBOL ligand **L10**/LiOPh in the enantioselective addition of malonate and acetate nucleophiles to *β*-nitrostyrene (Scheme 276).[557] Although the addition of ethylmalonate gave only the racemic 1,4-adduct, up to 99% of enantioselectivity was reached in the case of ethyl acetoacetate, but in a 1/1 ratio for the resulting diastereoisomers.



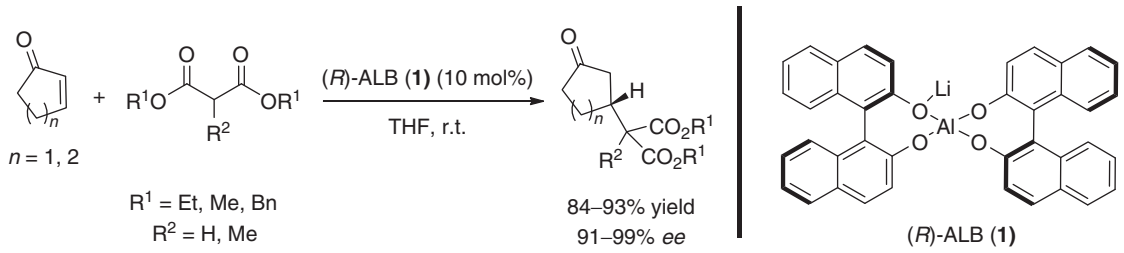
Scheme 276 Chiral (S)-BIMBOL-lithium salt in the enantioselective addition of malonate and acetate nucleophiles to *β*-nitroolefins.

4.04.11 Al/Ga Metal-Catalyzed Enantioselective Conjugate Addition

4.04.11.1 ACA with Cyclic and Acyclic Enones

4.04.11.1.1 Addition of β-dicarbonyl compounds and related malonate nucleophiles

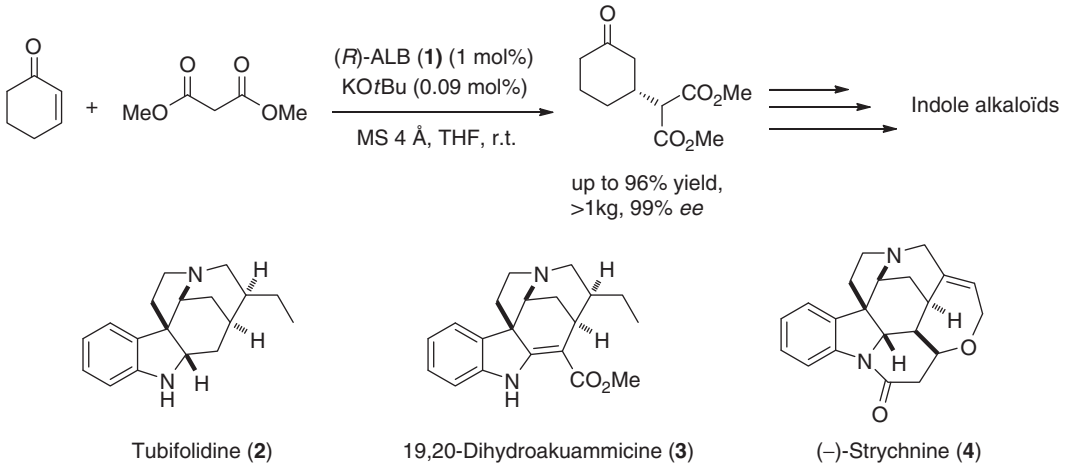
In 1996, Shibasaki and coworkers reported the first aluminum-based asymmetric catalyst.[566] Indeed, the extension of the heterobimetallic concept, initially described with rare earth metal (see Section 4.04.6), led to efficient catalytic asymmetric reactions promoted by the aluminum-lithium-BINOL (ALB) catalyst **1**. The ALB catalyst **1**, easily prepared from 1 equivalent of $LiAlH_4$ and 2 equivalents of BINOL, was first described in the efficient asymmetric Michael addition of malonate derivatives with cyclic enones (Scheme 277).



Scheme 277 ALB-catalyzed asymmetric Michael addition.

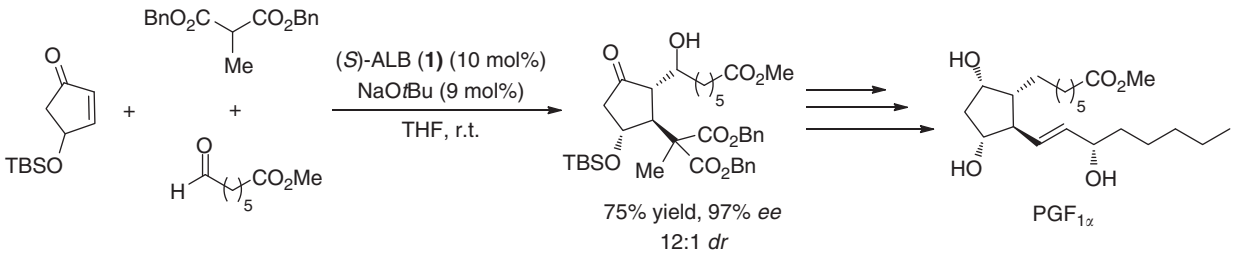
Soon after, it was demonstrated that these reactions were greatly accelerated by an addition of alkali metal reagent (base) to obtain products with very high enantioselectivities.[567] Within the same reaction, the combined use of Ga-Na-Binol and NaO*t*-Bu evidenced enhanced reaction rates (50 times faster) than with Ga-Na-Binol alone. Notably, this activation method greatly improved the asymmetric Michael addition of cyclohexenone and dimethylmalonate catalyzed by ALB,[568] with applications in the synthesis of indole alkaloids: tubifolidine (**2**),[569] 19,20-dihydroakuammicine (**3**),[570] and (–)-strychnine (**4**) (Scheme 278).[571,572]

Interestingly, Shibasaki and coworkers anticipated the possibility of trapping the Al-enolate by an electrophilic aldehyde and could obtain the desired three-component coupling product with high efficiency.[566] This strategy combined with kinetic resolution



Scheme 278 ALB-catalyzed asymmetric synthesis of indole alkaloids.

allowed for the asymmetric synthesis of prostaglandin (PG) precursors (Scheme 279).[573] The kinetic resolution with 4-O-protected cyclopentenones was further evaluated and employed in the synthesis of a HIV protease inhibitor.[574]



Scheme 279 Cascade asymmetric Michael–Aldol with kinetic resolution.

Other types of aluminum complexes were developed to promote ACA. Sundararajan and coworkers described the C_2-symmetric heterobimetallic catalyst **L2** and achieved high yields and enantioselectivities in the Michael addition of dicarbonyl nucleophiles with cyclic and acyclic enones.[575] Although low enantioselectivities were obtained with chiral ligand **L3** derived from tartaric acid,[576] good yields and up to excellent enantiomeric excesses were achieved with the amino ester-derived ligand **L4** for the Michael addition of diethylmalonate to cyclohexenone (Figure 20).[577]

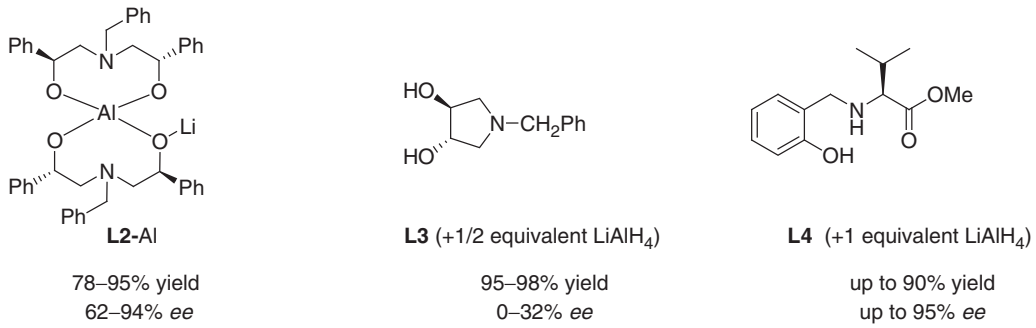
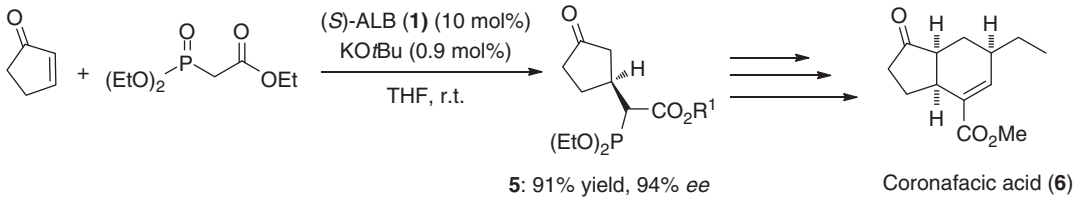


Figure 20 Al-catalytic systems for ACA with enones.

The Shibaski group also reported the efficient replacement of malonate substrate by a Horner–Wadsworth–Emmons reagent. The desired Michael adduct **5**, a precursor of coronafacic acid **6**, was obtained with high yield and enantioselectivity (Scheme 280).[578]

Tremendous effort has been given to the immobilization of the heterobimetallic ALB catalyst. Sasai and coworkers reported the first immobilization of a heterobimetallic multifunctional asymmetric catalyst using conjugate polymeric BINOL derivatives.[579] High yield and enantiomeric excess were obtained for the Michael addition of dibenzylmalonate to cyclohexenone in the presence



Scheme 280 ACA of Horner–Wadsworth–Emmons reagent.

of the reusable catalyst **L5**-Al. In the same context, polystyrene-supported (**L6**),[580] dendrimer-supported (**L7**),[581] and metal-bridged polymer (**L8**)[582] heterobimetallic catalysts have evidenced interesting catalytic behaviors and recyclability potentials (Scheme 281).

4.04.11.1.2 Conjugate addition of nitriles and nitroalkanes

Feringa and coworkers reported the ACA of α-nitroesters with acyclic enones catalyzed with the ALB heterobimetallic catalyst (Scheme 282).[583]

Interestingly, Feng and coworkers reported enantioselective Michael addition of malonitrile to chalcones catalyzed by a simple quinine-Al(O*i*-Pr)$_3$ complex. High yields and high enantioselectivities were achieved with a broad range of linear enones to generate the chiral desired products, which are precursors of biologically active 4H-pyran compounds (Scheme 283).[584] Recent theoretical investigations evidenced a dual activation mechanism in the presence of a cinchona alkaloid aluminum(III) complex.[585]

Salen–aluminum complexes constitute an important class of catalysts able to promote efficient enantioselective 1,4-addition of a variety of nucleophiles to a broad range of α,β-unsaturated systems. Despite low enantioselectivities observed for Michael addition of diketoesters with cyclic enones,[586] high efficiency was achieved for the conjugate addition of nitroalkanes (Scheme 284) and α-cyanoesters to acyclic enones (Scheme 285).[587]

4.04.11.1.3 Addition of indoles with enones

In 2003, Bandini et al. reported the ECA of indoles with α,β-unsaturated ketones catalyzed by a salen–AlCl complex.[588] The desired alkylated indole products were obtained in good yields and enantioselectivities in the presence of 2-6-lutidine as additive (Scheme 286).

4.04.11.1.4 Addition of hetero-nucleophiles with enones

In 2004, Jacobsen and coworkers reported the ECA of hydrazoic acid to α,β-unsaturated ketones catalyzed by a salen–AlO complex. The desired β-azido ketones products were readily converted into chiral β-amino ketones via reduction and can also undergo [3+2] cycloaddition with alkynes (Scheme 287).[587] Interestingly, similar motifs can also be obtained via ECA of *N*-heterocycles.[589] Indeed, high enantiocontrol was attained with purine, benzotriazole, tetrazole, benzimidazole derivatives, and α,β-unsaturated ketones bearing aliphatic β-substituents (Scheme 288).

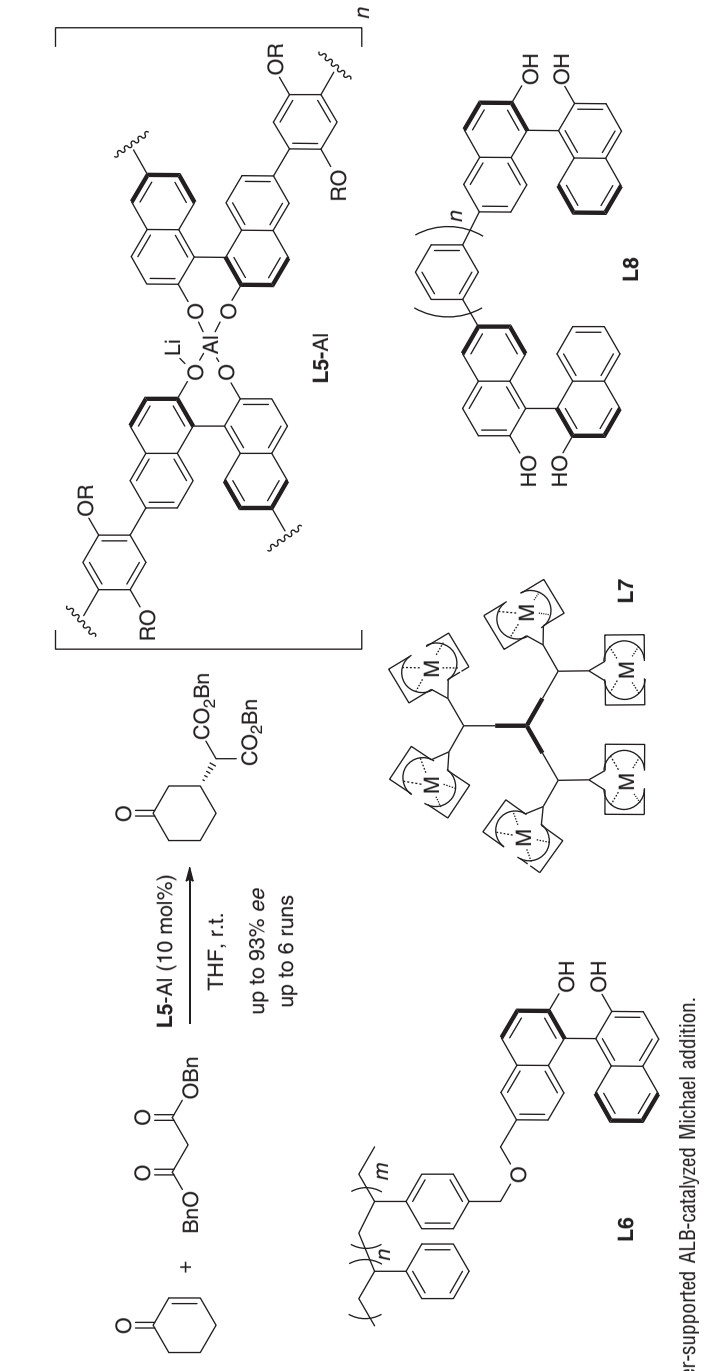
4.04.11.2 ACA with Nitroolefins

Nitroolefins are versatile intermediates in organic synthesis. In 2008, Namboothiri and Rai described the enantioselective conjugate addition of dialkyl phosphates to nitroalkenes. The catalytic system based on a heterobimetallic ALB complex produced β-nitrophosphonates in modest to good yields with high enantioselectivities (Scheme 289).[590]

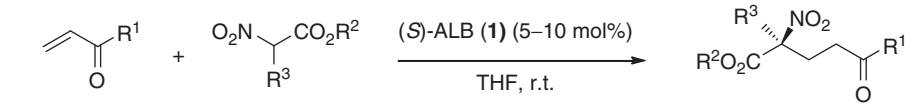
4.04.11.3 ACA with α,β-Unsaturated Imides

4.04.11.3.1 Cyanide addition

The asymmetric 1,4-addition of cyanide to α,β-unsaturated carbonyl compounds provides access to useful chiral building blocks. In this context, Jacobsen and coworkers developed an efficient methodology for the conjugate addition of cyanide to α,β-unsaturated imide catalyzed by salen–Al(III) complexes. Indeed, the desired cyanide adducts were prepared with high yields and enantioselectivities in the presence of HCN generated *in situ* from TMSCN and 2-propanol (Scheme 290).[591] Interestingly, enhanced reactivity and similar or better enantioselectivities were evidenced with a cooperative dual catalysis system combining a chiral salen–Al^{III} and a Pybox-Er^{III} complex.[477] Although, β-alkyl substituted imides are efficient substrates, no reaction was observed with imide derivatives bearing unsaturated β-substituents (R = aryl, vinyl, alkynyl). This limitation was overcome with the dinuclear salen–Al complex (Figure 21).[592] Additionally, Weck and coworkers reported highly active reusable polymer-supported salen–Al catalysts for the ECA of cyanide.[593]



Scheme 281 Polymer-supported ALB-catalyzed Michael addition.

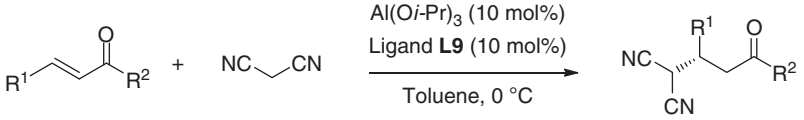


R^1 = Me, Et, Ph

R^2 = Et, Bn
R^3 = Me, Et

81–87% yield
up to 80% *ee* with $R^1 = R^3$ = Me, R^2 = Bn

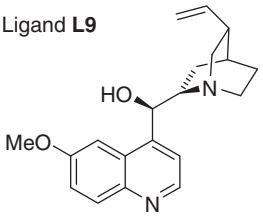
Scheme 282 ALB-catalyzed ACA with α-nitroesters.



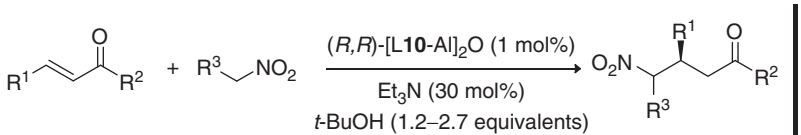
R^1 = Ar, PhCH=CH, ^{t}Bu, C_6H_{11}, 2-thienyl
R^2 = Ar, 2-thienyl

72–95% yield
77–93% *ee*

Ligand **L9**



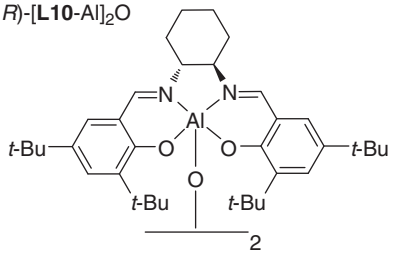
Scheme 283 ALB-catalyzed ACA with α-nitroesters.



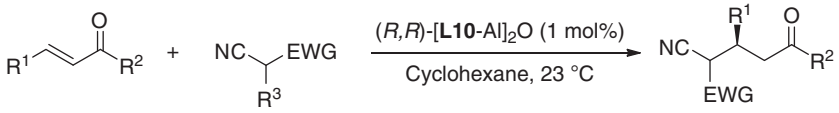
R^1 = Ar; R^2 = CH_3, *n*-Bu, *i*-Pr
R^3 = H, CH_3

70–90% yield
88–95% *ee*

(*R,R*)-[**L10**-Al]$_2$O



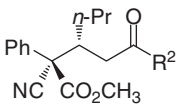
Scheme 284 Enantioselective conjugate addition of nitroalkanes with salen–Al complex.



R^1 = Ph, CH_2CH_2OBn, *t*-Bu, *n*-Pr, 2-thienyl
R^2 = Ph, CH_3, *n*-Bu, *i*-Pr
R^3 = H; EWG = CO_2CH_3, CN, SO_2Ph

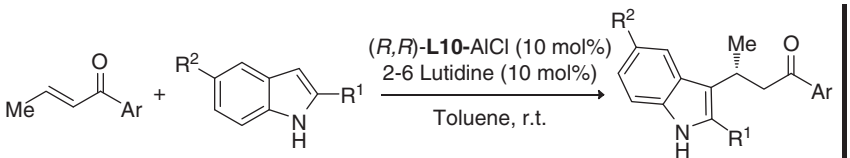
76–93% yield
and
75–96% *ee*

With R^3 = Ph and 2.5 mol% (*S,S*)-**L10**



88% yield; >30:1 *dr*
89% *ee*

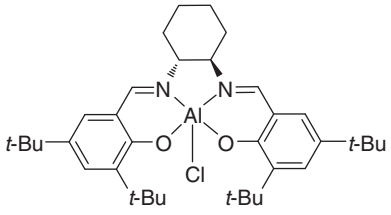
Scheme 285 Enantio- and diastereoselective conjugate addition of α-cyanoesters with salen–Al complex.



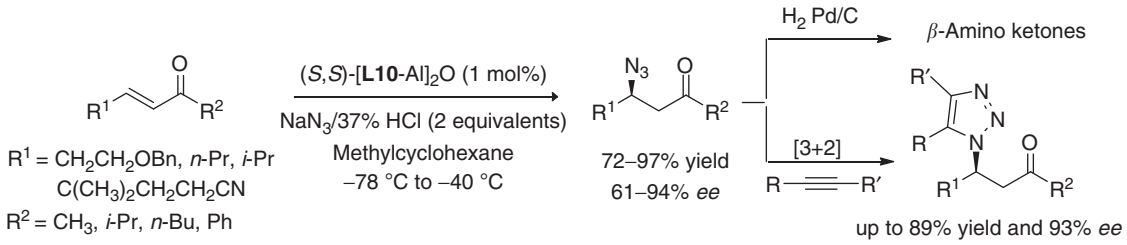
R^1 = H, Me; R^2 = H, OMe

35–95% yield
49–89% *ee*

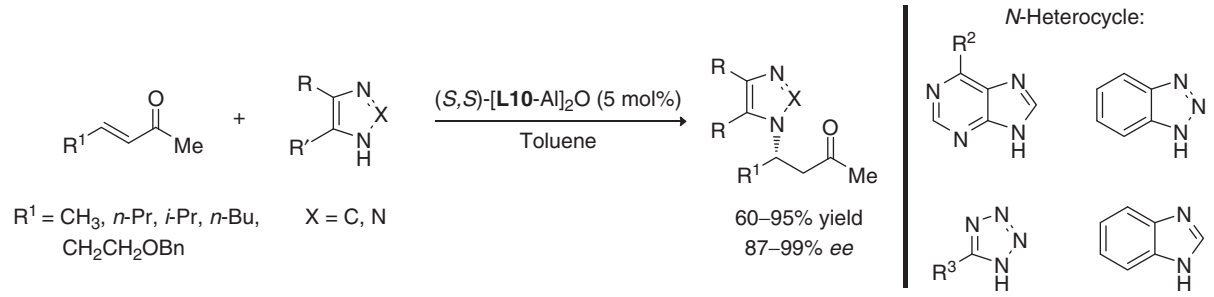
Ligand (*R,R*)-**L10**-AlCl



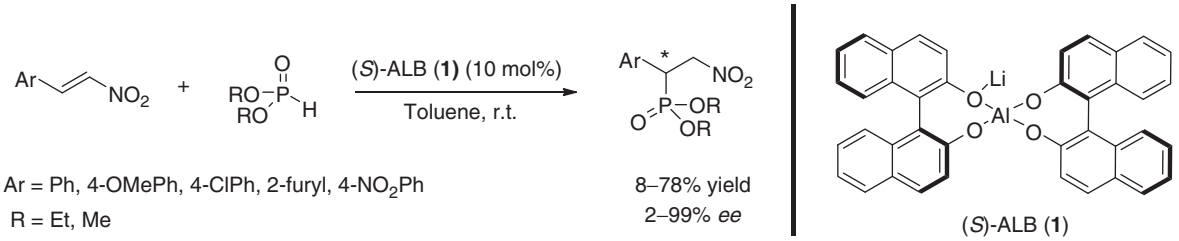
Scheme 286 Enantioselective conjugate addition of indoles with salen–Al complex.



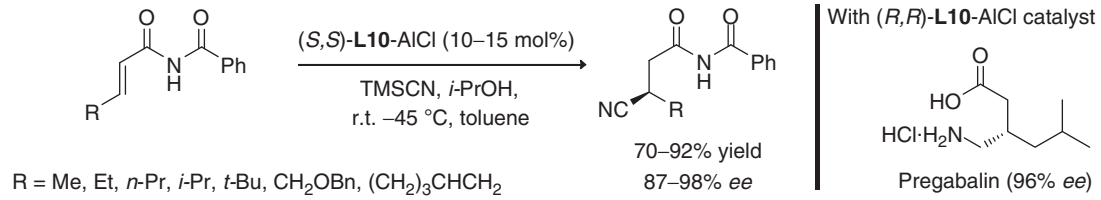
Scheme 287 Conjugate addition of hydrazoic acid to acyclic enones with salen–Al complex.



Scheme 288 Conjugate addition of *N*-heterocycles to acyclic enones with salen–Al complex.



Scheme 289 ALB-catalyzed ACA of dialkyl phosphates to nitroalkenes.



Scheme 290 ACA of cyanide to imides.

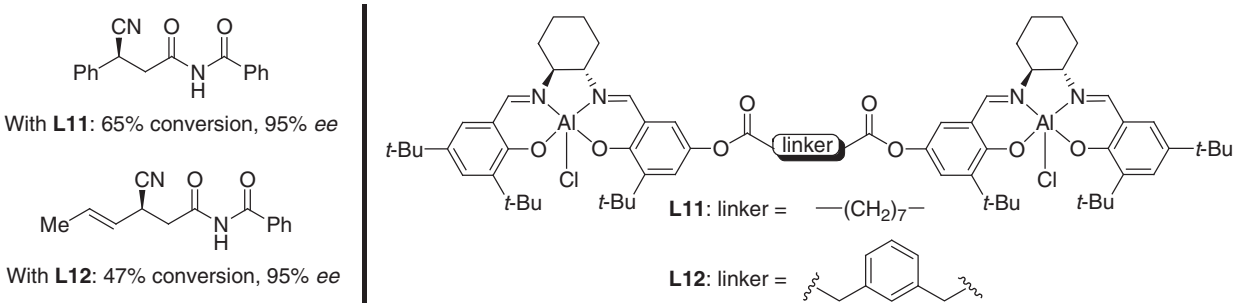
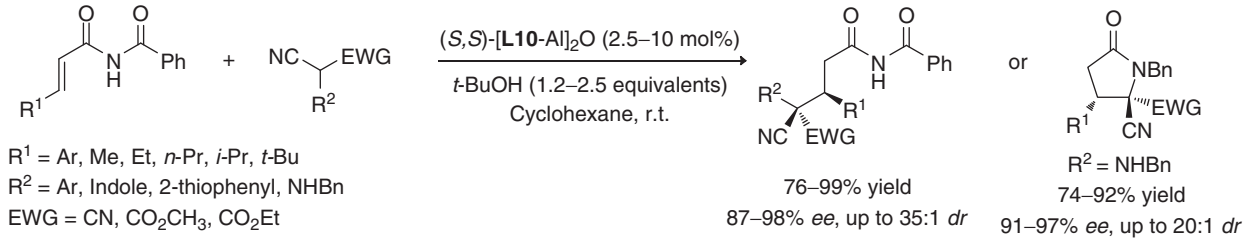


Figure 21 Dinuclear salen–Al complexes catalyzed 1,4-addition of cyanide.

4.04.11.3.2 Addition of nitrile derivatives with α,β-unsaturated imides

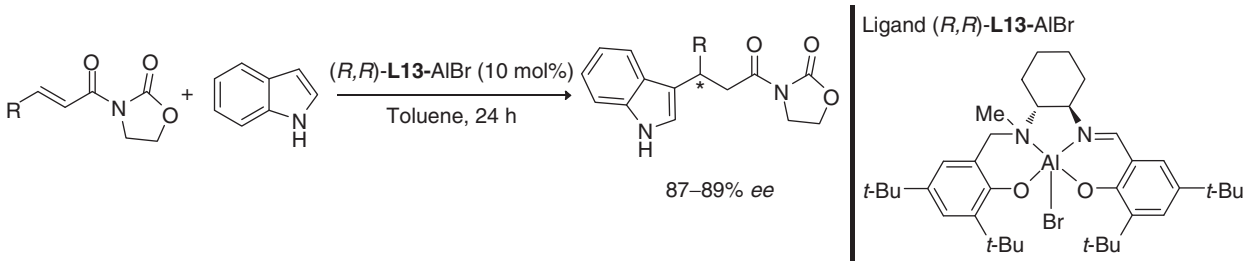
Aluminum–salen complexes have been identified as efficient catalysts for the asymmetric Michael addition of nitrile nucleophiles with α,β-unsaturated imides.[594] Substituted cyanoacetate derivatives offered formation of quaternary stereocenters with high diastereoselectivities and enantioselectivities. Moreover, chiral γ-lactams were prepared with (*N*-benzylamino)-substituted cyanoacetate (Scheme 291). This efficient methodology was later applied to α,β-unsaturated β-silyl imide for the total synthesis of a γ-lactam-containing natural product, lactacystin, a proteasome inhibitor.[595]



Scheme 291 Salen–Al-catalyzed enantioselective Michael addition of nitrile with α,β-unsaturated imides.

4.04.11.3.3 Friedel–Crafts reaction of indole with α,β-unsaturated imides

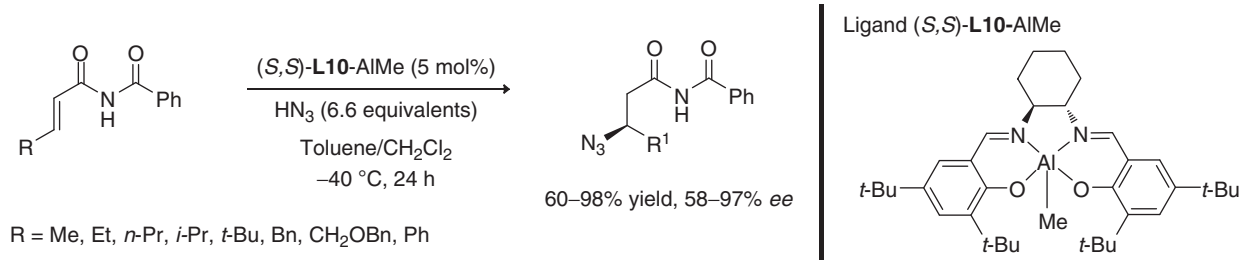
Recently, Katsuki and coworkers reported the Friedel–Crafts reaction of indole with α,β-unsaturated imides catalyzed by a salalen–aluminum complex. The desired alkylated indole products were obtained with excellent enantioselectivity (Scheme 292).[596]



Scheme 292 Salalen–Al-catalyzed enantioselective Friedel–Crafts reaction of indole with α,β-unsaturated imides.

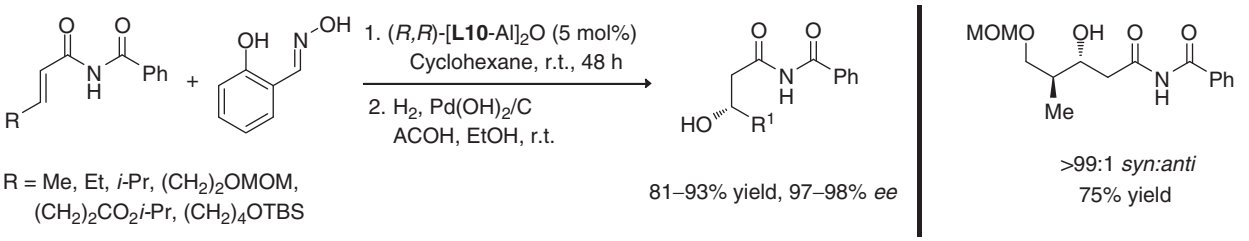
4.04.11.3.4 Addition of hetero-nucleophiles with α,β-unsaturated imides

In 1999, Jacobsen and Myers reported the first example of efficient ACA with aluminum–salen complex.[597] Indeed, high yields and enantioselectivities were achieved for the 1,4-addition of hydrazoic acid to unsaturated imides in the presence of a salen–Al(III) catalyst (Scheme 293). Similarly, *N*-heterocycle nucleophile such as purine, benzotriazole, and tetrazole derivatives were efficiently employed in the ECA to unsaturated imides in the presence of a salen–Al catalyst.[589]



Scheme 293 Conjugate addition of hydrazoic acid to unsaturated imides with salen–Al complex.

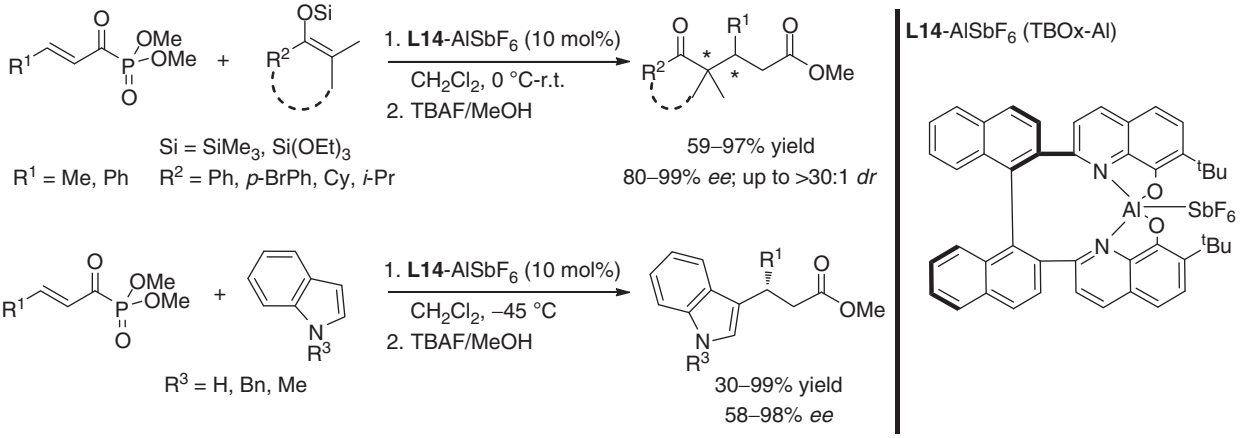
The same group described the development of the catalytic asymmetric oxygen-centered addition of salicylaldoxime to α,β-unsaturated imides catalyzed by a salen–aluminum complex (Scheme 18).[598] This reaction represents a rare example of formal enantioselective hydration of electron-deficient alkenes (Scheme 294).



Scheme 294 Enantioselective formal hydration of unsaturated imides with salen–Al complex.

4.04.11.4 ACA with Unsaturated Acyl Phosphonates

In 2007, Yamamoto and coworkers reported an efficient Mukayama–Michael reaction between silyl enol ether and α,β-unsaturated acyl phosphonates. Interestingly, the newly developed tethered bis(8-quinolinolato)-aluminum complex (TBOxAl) catalyzed effectively the reaction of tetrasubstituted enolates to provide chiral all-carbon-quaternary centers (Scheme 295).[599] Interestingly, this chiral aluminum catalyst was also able to promote with efficiency the enantioselective Friedel–Crafts alkylation of indole.



Scheme 295 Asymmetric addition with α,β-unsaturated acyl phosphonates catalyzed by (TBOx)Al complex.

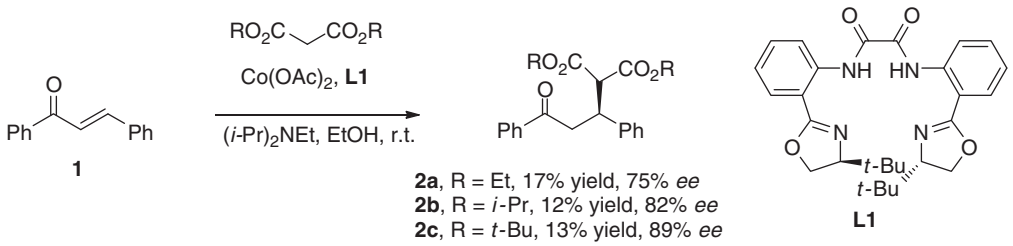
4.04.12 Miscellaneous Metal-Catalyzed Enantioselective Conjugate Addition

Few publications reported the utilization of other metals to achieve catalytic additions of nucleophiles to electron-deficient alkenes in an enantioselective fashion. These miscellaneous metals are cobalt, iron, manganese, silver, cadmium, and indium.

4.04.12.1 Cobalt

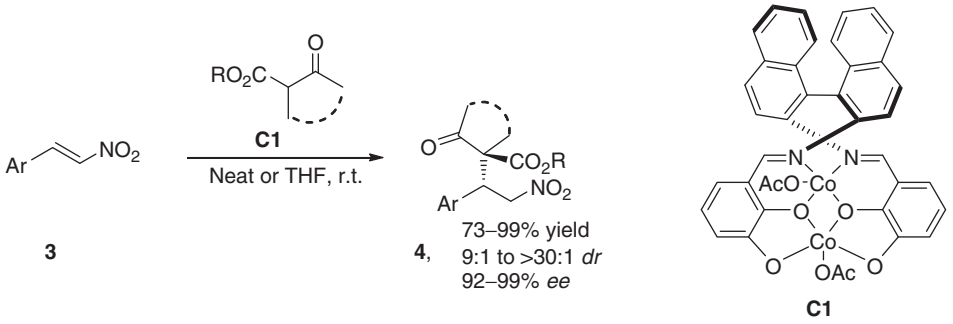
Cobalt was mainly utilized to perform enantioselective Michael additions to α,β-unsaturated ketones. In 1984, pioneering works of Brunner demonstrated that a catalytic system generated *in situ* from $Co(acac)_2$ and (+)-1,2-diphenylethylenediamine as chiral ligand was able to catalyze the addition of methyl 1-oxo-2-indanecarboxylate to MVK with an optical induction of 66%.[600a] Unfortunately, attempts to improve optical yields of the Michael addition of 1,3-dicarbonyl compounds by testing other ligands such as alkaloid or salicylaldimine derivatives,[600b,c] proline-based ligands,[601] or spirobiindane-containing ligands[602] were unsuccessful for many years. Nevertheless, Pfaltz was the first to demonstrate that a cobalt-based system allows to get a Michael adduct with a high enantiomeric excess (up to 89%, Scheme 296).[603] Tertio-butyl-substituted chiral bisoxazoline oxalamide **L1** was found to provide good enantioselectivities as a function of the steric hindrance of malonate derivates but with low chemical yields.

Matsunaga and Shibasaki reported an efficient example of bifunctional cooperative asymmetric catalysis using a homodinuclear biscobalt(III)–Schiff base complex for the conjugate addition of β-ketoester to nitroolefins.[604] Using a dinucleating Schiff base, several combinations of metals were tested to identify the most powerful system promoting enantioselective Michael addition. Cu, Pd, Ni, Mn, Zn, or lanthanides were tried with more or less success; only a bisnickel system gave rise to Michael



Scheme 296 Enantioselective cobalt-mediated Michael addition of malonates to chalcone.

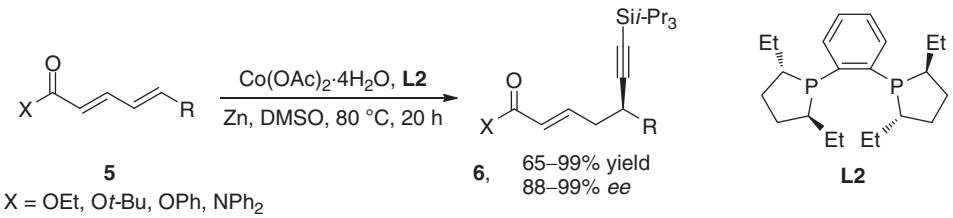
adducts with good *ee*s (75%). However, biscobalt(III) complex **C1** promoted the addition in excellent yield with both good diastereo- and enantioselectivity (Scheme 297). An interesting feature of this catalytic system is that it also performed well in the absence of solvent and the catalyst loading could be decreased down to 0.1 mol%. Mechanistic studies and control experiments were carried out to confirm the intramolecular cooperative effect of the two cobalt centers.



Scheme 297 Asymmetric 1,4-addition of β-ketoesters to nitroalkene catalyzed by a bifunctional homobimetallic Co_2–Schiff base complex.

Recently, Feng and Liu investigated a tandem asymmetric Michael addition-cyclization reaction to prepare chiral 4*H*-chromene compounds.[605] The enantioselective Michael addition of cyclohexane-1,3-dione and dimedone to 2-cyanoacrylate derivatives was achieved using salen-based catalysts. Among the metal salts scrutinized, only cobalt(II) acetate afforded moderate enantioselectivity. After an optimization process, the tandem reaction was found to display a good asymmetric induction, between 71% and 89% *ee* for various Michael acceptors.

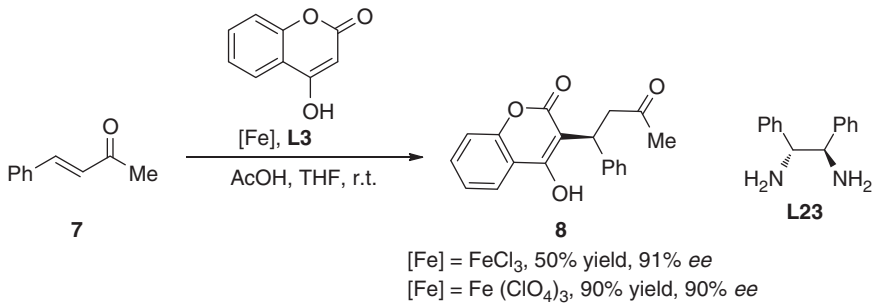
Other nucleophiles than 1,3-dicarbonyl compounds were studied to accomplish cobalt-catalyzed enantioselective addition. Feringa reported the addition of diethyl zinc to chalcone **1** mediated by $Co(acac)_2$ and chiral amino alcohols.[606] The best result, 83% *ee*, was obtained by a (+)-camphor-based ligand. Recently, Nishimura and Hayashi studied the cobalt-catalyzed asymmetric conjugate alkynation of α,β-unsaturated ketones and $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds.[607] Having developed a cobalt-based catalytic system to achieve the conjugate addition of silylacetylenes to enones using a bidentate ligand – diphenylphosphino (ethane) (dppe) –, the set up of an asymmetric version was accomplished using a chiral bisphosphine ligand – (2*S*,4*S*)-2,4-bis (diphenylphosphino)pentane. Several β-alkynyl-ketones were isolated in high yields and *ee*s spanning from 79% to 91%. Soon after, the catalytic system was reinvestigated for asymmetric addition of terminal alkynes to extended conjugate systems (Scheme 298). A thorough screening of chiral bisphosphine ligands identified (*S*,*S*)-Et-duphos **L2** as providing the best chiral induction. The addition of (triisopropylsilyl)acetylene to dienoate and dienamides **5** occurred exclusively in the δ-position affording 1,6-conjugate adducts **6** in good yields and high enantioselectivities. An $\alpha,\beta,\gamma,\delta$-unsaturated arene was also found to be a good substrate in the alkynylated product obtained in 68% yield and 88% *ee*. Control experiments proved the imperative need of zinc to form adducts and the influence of the geometrical structure of the starting material on both chemical and optical yields.



Scheme 298 Cobalt-mediated asymmetric 1,6-conjugate addition of (triisopropylsilyl)acetylene to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds.

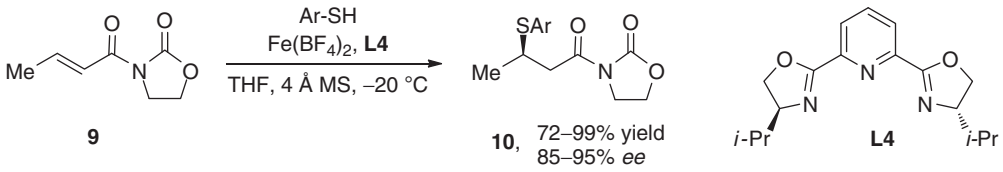
4.04.12.2 Iron

Over the last two decades, iron has witnessed impressive advances in homogenous catalysis as a result of intensive researches. Nevertheless, iron-promoted enantioselective nucleophilic additions to electron-deficient alkenes remain a restricted topic with only few examples of asymmetric Michael addition using C-, O-, or S-nucleophiles and Friedel–Craft alkylations. In 2010, Lai and coworkers studied the Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one **7** (Scheme 299).[608] The screening of various iron salts and chiral amines or amino alcohols led to the finding that a combination of iron(III) salts, either $FeCl_3$ or $Fe(ClO_4)_3$ with the (+)-1,2-diphenylethylenediamine **L3**, proceeded smoothly to the formation of chiral warfarin **8** with excellent enantioselectivity (up to 91% *ee*) and an isolated yield moderate to good as a function of the iron salt used.



Scheme 299 Iron-catalyzed enantioselective addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one **7**.

The oxa-Michael addition of oxime to α,β-unsaturated aldehydes was investigated in an enantioselective manner using chiral *N*,*N*′-dioxide–iron(II) complexes.[609] Unfortunately, despite the inspection of structurally different chiral *N*,*N*′-dioxide ligands and additive effect, oxa-Michael adducts were obtained in moderate yields and relatively good enantioselectivites (up to 76% *ee*). Better successes were obtained for the sulfa-Michael addition of thiophenol compounds to (*E*)-3-crotonyloxazolidin-2-one **9**.[610] As depicted in Scheme 300, the $Fe(BF_4)_2$/pyridine (bis)oxazoline **L4** catalyst promoted efficiently the addition thiols to **9**. Only thiophenol nucleophiles gave high *ee* values (up to 95% *ee*). Slight modifications of the ligand structure have been made to improve the chiral induction, however, each time the racemic adduct was isolated. Of note, cobalt salts can replace iron without any significant alteration to enantioselectivity.



Scheme 300 Iron-catalyzed enantioselective sulfa-Michael addition.

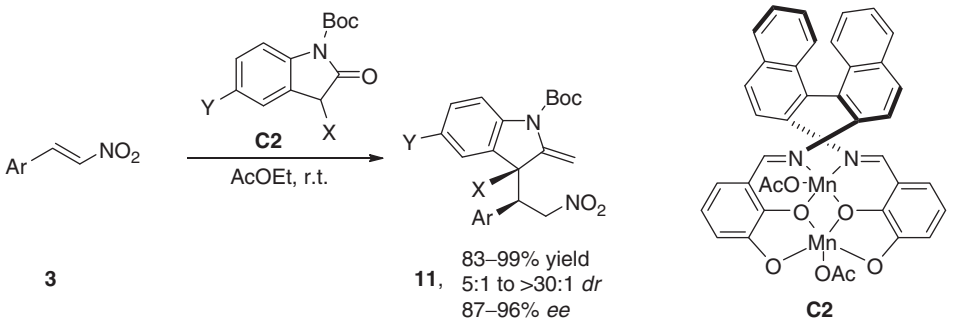
Xia and Huang developed a cooperative catalytic system for the Friedel–Crafts alkylation by the combination of an iron salt and a chiral phosphoric acid, which acts as a ligand and a proton source.[611] Thus, enantioselective additions of indoles to β-aryl-α'-hydroxy enones were carried out with good to excellent yields and good enantioselectivities.

4.04.12.3 Manganese

To the best of our knowledge, a single report mentions the utilization of manganese to achieve enantioselective nucleophilic additions to electron-deficient alkenes.[612] During their work on bimetallic Schiff base catalysis, Matsunaga and Shibasaki tested various combinations of metals to perform enantioselective additions of nucleophiles to nitroolefins. Although the CO_2–Schiff base complex **C1** was found competent for β-ketoester nucleophiles, oxindole nucleophiles gave low yields and *ee*s. To find a suitable catalyst, other metals were screened, and the $Mn(III)_2$–Schiff base complex **C2** gave the best reactivity, diastereo-, and enantioselectivity (Scheme 301). This conjugate addition using complex **C2** was found broad in scope with *ee* values spanning from 87% to 96% for adducts **11**. Additional experiments indicated that the two manganese atoms are essential to reach high stereoselectivity and reactivity.

4.04.12.4 Silver

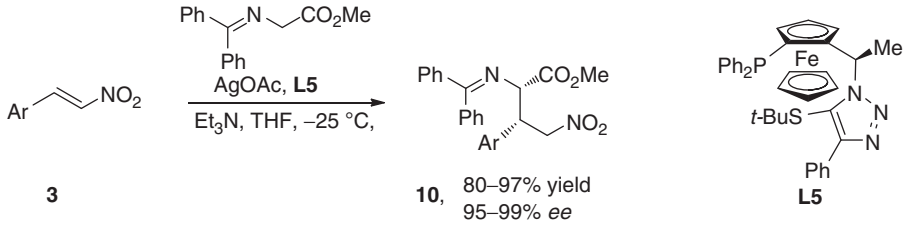
Phosphine silver complexes are known to promote efficiently various Michael additions.[613] However, few examples of enantioselective variants have been reported. Kobayashi and Shirakawa studied the ACA of a β-ketoester to nitroalkenes catalyzed



Scheme 301 Asymmetric 1,4-addition of oxindoles to nitroalkene catalyzed by a bifunctional homobimetallic Mn_2–Schiff base complex.

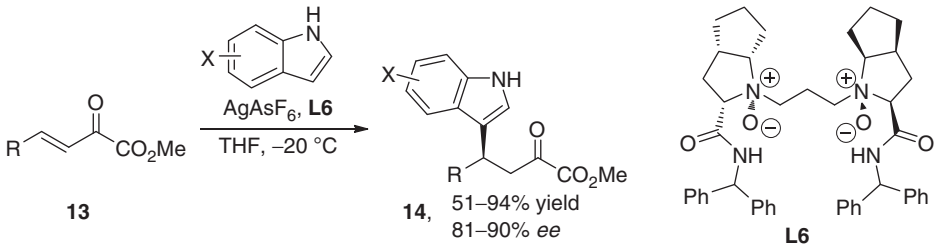
by (*R*)-Tol-BINAP·AgOTf in water.[614] With cyclopentanone-2-carboxylic *tert*-butyl ester and *trans*-β-nitrostyrene as substrates, the corresponding Michael adduct was isolated in 71% yield and a 77:23 mixture of two diastereomers. The major diastereomer indicated 78% *ee*.

Following their work on asymmetric Mannich reaction using glycine imino esters as nucleophiles, Fukuzawa and coworkers investigated the chiral catalytic system silver/ThioClickFerrophos **L5** to other applications.[615] As presented in **Scheme 302**, the catalytic system AgOAc/**L5** promoted successfully the ACA of benzophenone glycine imino ester to various nitroolefines **3**. Of note, significant amounts of [3+2] cycloadducts were isolated in the same time than Michael adducts **12**. Using Et_3N as additive allowed to get exclusively *anti*-α-imino-γ-nitrobutyrates **12**, precursors of α,γ-diamino acids, with excellent reactivities, diastereo-, and enantioselectivities.



Scheme 302 ACA of glycine imino ester to nitroalkenes mediated by silver.

Among the asymmetric transformations Feng investigated using chiral *N*,*N*′-dioxide ligands, the enantioselective Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-ketoesters is of interest.[616] This is a rare example of central metal-controlled reversal of asymmetry in enantioselective reaction. The metal screening for the enantioselective Friedel–Crafts alkylation of indoles to β,γ-unsaturated α-ketoesters **13** showed that with the same chiral ligand **L6**, silver salts led to the formation of (*S*)-enantiomer of adduct **14**, whereas samarium salts generated preferentially (*R*)-enantiomer (**Scheme 303**). The authors suggested that the difference in the coordination number between Ag(I) and Sm(III) leads to distinctive transition states and changes the face of indole's attack. Overall, good yields and enantioselectivities were obtained for a variety of indoles and β,γ-unsaturated α-ketoesters **13**.

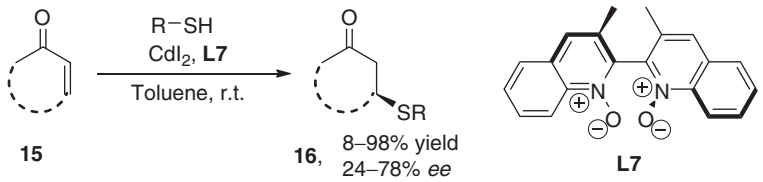


Scheme 303 Silver-catalyzed enantioselective Friedel–Crafts alkyation.

4.04.12.5 Cadmium

Owing to its high toxicity, cadmium was little used to carry out catalytic metal-mediated transformations. Only Nakajima explored this metal to sulfa-Michael addition of cyclic α,β-unsaturated ketones and acyclic α,β-unsaturated aldehydes.[617] Various metal salts

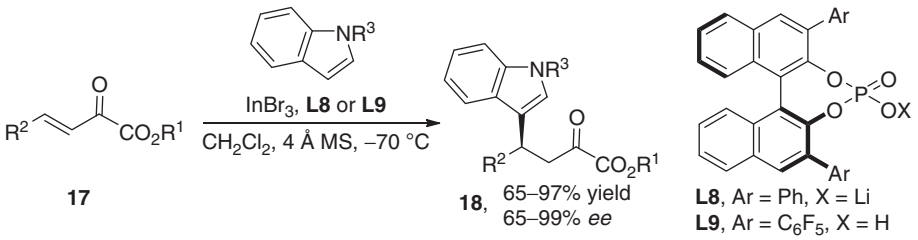
were tested in association with chiral *N,N′*-dioxide ligand **L7** and cadmium(II) iodide showed the best skill to get the cyclohexenone adduct with the highest stereoinduction. Toxicity issues can be balanced by the low loading of metal used (down to 1 mol%). Unfortunately, the catalytic system CdI_2/**L7** was found to be very substrate-dependent with fluctuating yields and *ee* values from 24% to 78% for products **16** (Scheme 304). The same trend was observed with *α,β*-unsaturated aldehydes as Michael acceptors.



Scheme 304 Cadmium-catalyzed asymmetric sulfa-Michael addition.

4.04.12.6 Indium

Indium was often tested as the metal source to achieve enantioselective Michael additions or Friedel–Crafts alkylations, but was generally supplanted by rare earth elements such as scandium or lanthanum. However, Luo proved that $InBr_3$ as metal precursor when combined with chiral phosphoric acids as ligands **L8** or **L9** was able to catalyze efficiently the Friedel–Crafts alkylation of indole to *β,γ*-unsaturated *α*-ketoesters **17** (Scheme 305).[618] Thus, 1,4-adducts **18** were isolated with moderate to good optical purities and yields. Interestingly, the use of InF_3 instead of $InBr_3$ allowed to form selectively 1,2-adducts with high *ee*s.



Scheme 305 Indium-mediated enantioselection Friedel–Crafts alkylation using chiral phosphoric acid ligands.

4.04.13 Conclusion and Outlook

This chapter has taken the readers on a tutorial tour through the landscape of metal-catalyzed asymmetric nucleophilic additions to electron-deficient alkenes in which copper-mediated conjugate additions occupy a special place. Indeed, the addition of zinc reagents to *α,β*-unsaturated carbonyl compounds has been extensively used as the benchmark reaction to gauge the enantioselective potential of new chiral ligands. Nevertheless, this transformation witnessed groundbreaking advances since few years with the use of various nucleophiles: not only organomagnesium, organoaluminum, organoboron, or silyl reagents but also with the employment of more and more intricate substrates allowing asymmetric 1,6- and 1,8-conjugate additions. This is of note in that both ligands and nucleophiles played key roles in these developments. To date, the main limitation of copper-catalyzed addition to electron-deficient alkenes lies in the use of phenyl and more generally aromatic nucleophiles. However, this can be circumvented using chiral rhodium- or palladium-based catalytic systems. As presented along this chapter, a majority of the metals on the periodic table were investigated to perform asymmetric Michael additions of C-, N-, O-, and S-nucleophiles and Friedel–Crafts alkylations with variable success as a function of the metal and the ligand used. Despite undeniable achievements, compared to copper, other metals are currently in their infancy. In summary, within 20 years, tremendous progresses have been made in metal-catalyzed asymmetric nucleophilic additions to electron-deficient alkenes, but there is still room for improvements and new reactivity discoveries. We are convinced this enantioselective transformation has not ceased to surprise and amaze.

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4.05 Addition of H–X Reagents to Alkenes, Alkynes, and Allenes without Transition Metal

W Li and J Zhang, East China Normal University, Shanghai, P.R. China

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Glossary

Hydration The addition of H–OH to C–C multiple bonds.

Hydroalkoxylation The addition of RO–H bond to nonactivated C–C multiple bonds.

Hydroamination The addition of NR_2–H to C–C multiple bonds.

Hydrocarboxylation The addition of carboxylic acids to C–C multiple bonds.

Hydrohalogenation The addition of H–X (X = F, Cl, Br, and I) to C–C multiple bonds.

Ritter reaction The formation of *N*-alkyl carboxamides from aliphatic- or aromatic nitriles and carbocations.

4.05.1 Introduction

The importance of heterofunctionalization of unactivated carbon–carbon multiple bonds has been widely recognized in the field of carbon–heteroatom bond construction, and much effort has been made toward exploitation of this methodology. The direct

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addition of H–X reagents (where X = halogen, nitrogen, oxygen, sulfur, phosphorus, and selenium) across unsaturated carbon–carbon bonds to form one C–H bond and one C–X bond represents one of the most atom-economical processes for the synthesis of functionalized molecules. This chapter reviews the most representative reports from 1990 to 2012. Except a few examples of mercury- and gold-mediated reactions, metal-mediated addition of H–X to C–C multiple bonds and hetero-Michael reaction (X = nitrogen, oxygen, sulfur, etc.) of electron-deficient alkenes, alkynes, and allenes will not be covered in order to avoid the overlap with related chapters in this volume (*see* Chapters 4.01, 4.07, and 4.10).

4.05.2 Hydrogen Halides Addition

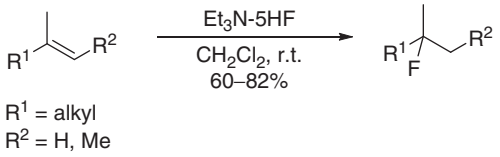
4.05.2.1 Introduction

Hydrohalogenation reaction is one of the most fundamental and yet more important reactions in organic synthesis. Generally, the reactivity order of hydrogen halide except HF parallels acidity order, which is HI > HBr > HCl. Aqueous HF is unreactive toward alkene and alkyne addition, whereas anhydrous HF is surprisingly reactive. However, hydrohalogenation reaction, especially the hydrobromination, may occur via the electrophilic addition process obeying Markovnikov rule or the radical chain process favoring anti-Markovnikov product. In recent years, various HX precursors have been developed for hydrohalogenation reaction.

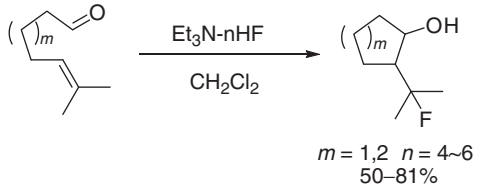
4.05.2.2 H–F Addition

4.05.2.2.1 Hydrofluorination of alkenes

Hydrofluorination of unsaturated carbon–carbon bonds is always accompanied by difficulties such as the handling of HF and undesirable polymerization of substrate. The use of less volatile solutions of HF with an organic base[1] such as acetone was first used by Bergstrom in the fluorination of double bonds in steroids.[2] Olah et al. later established that HF-30% (w/w) pyridine was a convenient reagent for the hydrofluorination of alkenes as well as other fluorination reactions.[3] Yoneda developed HF–melamine as less hygroscopic and superior to other HF–base solutions not only with regard to hydrofluorination activity for alkenes but also in relation to its preparation and ease of handling.[4] Et_3N–5HF has been developed in order to be a mild and selective hydrofluorination agent which can react with trisubstituted alkenes selectively, affording *tert*-alkyl fluorides without any influence on the functional groups such as the ketone or the alcohol moiety in the molecules (equation 1).[5] Hydrofluorinative cyclization of functionalized alkenes such as citroneral was also successfully carried out to produce five- or six-membered cyclic fluoro-compounds (equation 2).[6]



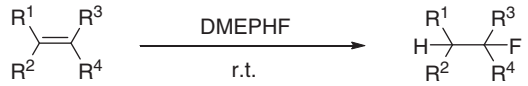
(1)

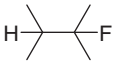
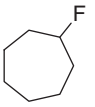
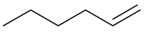
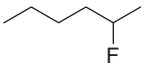
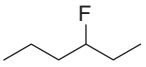
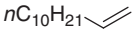
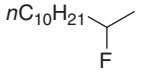
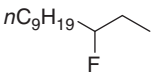
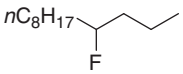
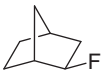


(2)

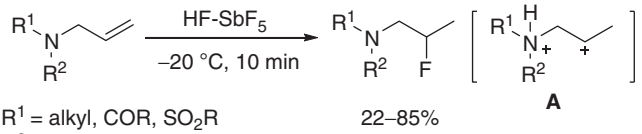
The dimethyl ether/poly(hydrogen fluoride) complex (DMEPHF) was found to be a convenient and effective fluorinating agent with an easy workup. The hydrofluorination of alkenes with DMEPHF proceeds smoothly at room temperature, giving the monofluoro products in good to excellent yields with high selectivity (**Scheme 1**).[7] Straight-chain alkenes gave isomeric secondary alkyl fluorides because of their ease of isomerization via a carbocation. However, this DMEPHF reagent cannot be used for the hydrofluorination of alkynes and highly active alkenes such as styrene derivatives due to their ability to initiate extensive polymerization.

Thibaudeau et al. found that *N*-allylic amines and sulfonamides react in the superacidic medium HF–SbF_5 to give β-fluoro nitrogen-containing compounds in moderate to good yields after a simple hydrofluorination reaction (equation 3).[8] The reaction was assumed to proceed via a superelectrophilic dication intermediate **A**. They also used this approach for the synthesis of methyl-substituted fluorinated amines along with a minor amount of fluorinated dimer (equation 4).[9]



Substrate	Time	Product	yield
	1		94%
	3		92%
	3		77%
	1		50%
			23%
	1		46%
			30%
			24%
	3		83%

Scheme 1 Hydrofluorination of alkenes with DMEPHF(1/5) reagent.



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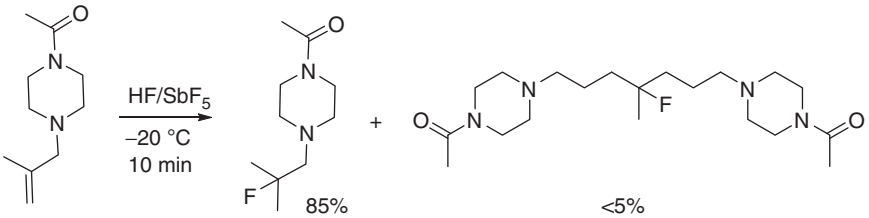
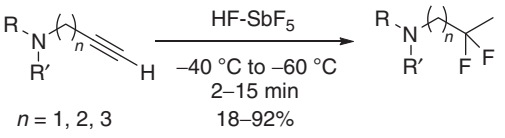


(4)

4.05.2.2.2 Hydrofluorination of alkynes

The addition of HF to alkynes can form either fluoroalkenes via monohydrofluorination or *gem*-difluoroalkanes via bis-hydrofluorination, which heavily depends on the electronic nature of alkynes and the reagents used. For example, Thibaudeau's group reported superacid-catalyzed synthesis of *gem*-difluoroamines from a variety of alkynylated amines, amides, and imides (equation 5).[10] This process also offers an effective route for the synthesis of difluorinated cinchona alkaloid derivatives. They proposed that these new difluoro derivatives were formed as a result of the electrophilic character of the intermediate dication (Scheme 2).



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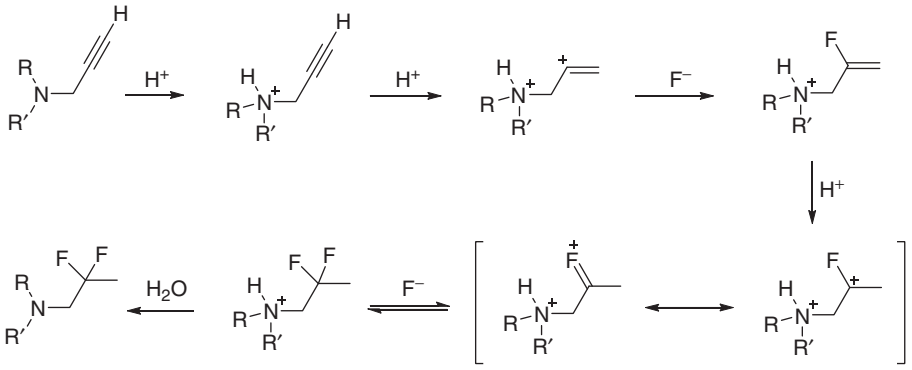
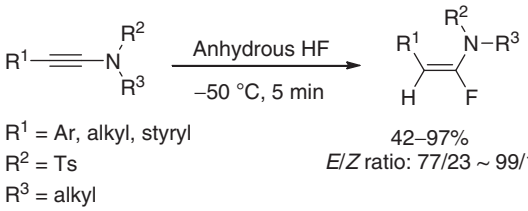


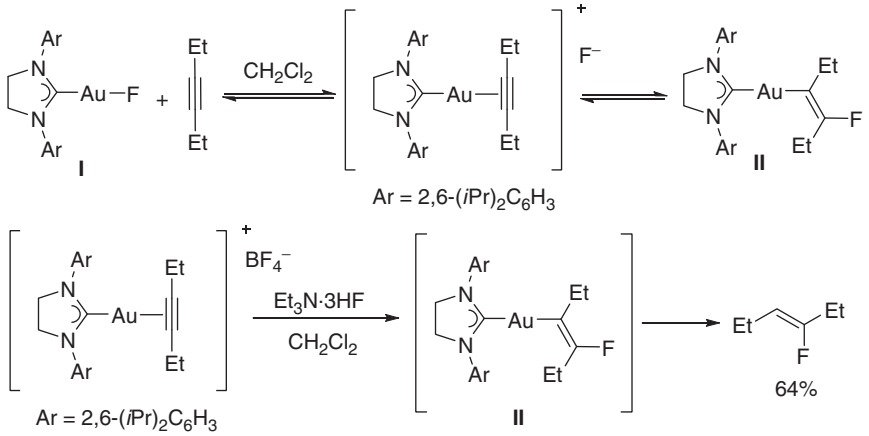
Scheme 2 Proposed mechanism.

Recently, a highly regio- and stereoselective *cis*-addition of HF to ynamides was developed by Thibaudeau et al., leading to *Z*-α-fluoroenamides via monohydrofluorination in 42–97% yields with up to 99/1 stereoselectivity (equation 6).[11] This reaction is applicable to a wide range of substrates according to the R^1 group.



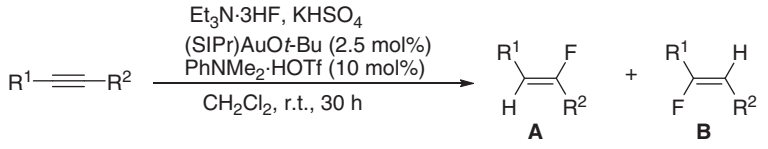
(6)

The Sadighi group first isolated the *N*-heterocyclic carbene (NHC)–gold(I) fluoride complex (**I**) in 2005 and studied the alkyne insertion reaction (Scheme 3). The reaction of an excess of 3-hexyne with this gold complex in CH_2Cl_2 led to β-(fluorovinyl)gold complex (**II**), whereas a complete recovery of gold(I) fluoride complex (**I**) was observed after removal of the solvent and alkyne, indicating this insertion reaction was reversible. When the performed cationic η^2-alkynylgold(I) complex was treated with $Et_3N{\cdot}3HF$, the desired hydrofluorinated alkene was detected in a 64% ^{19}F nuclear magnetic resonance yield.[12] The mechanism of this transformation most likely involves nucleophilic attack of the fluoride onto alkynes and subsequent protodemetalation of the resulting alkenyl gold complex.



Scheme 3 Reversible C–F formation.

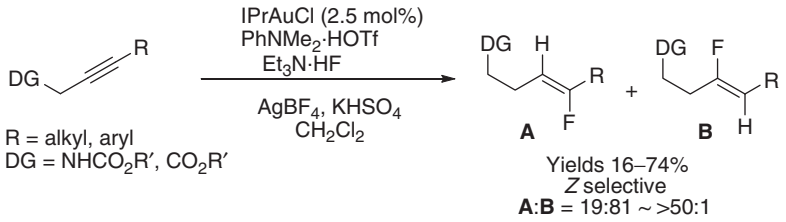
The *trans*-hydrofluorination of internal alkynes can also be achieved under the catalysis of electrophilic (NHC)–gold(I) complexes at room temperature, using the $Et_3N{\cdot}HF$ salt as a mild HF source. This reaction proceeds with an excellent regioselectivity even with a thiophene derivative (Scheme 4).[13]



Entry	R^1	R^2	Yield (%)	**A**:**B**
1	C_6H_5	C_6H_5	86	–
2	*n*-C_5H_{11}	*n*-C_5H_{11}	81	–
3	4-$MeOC_6H_5$	*n*-C_6H_{13}	63	5:1
4	C_6H_5	*n*-C_6H_{13}	78	13:1
5	4-$MeC(O)C_6H_5$	*n*-C_6H_{13}	82	**A** only
6		*n*-C_6H_{13}	74	**A** only

Scheme 4 Au-catalyzed hydrofluorination alkynes.

Further investigation carried out by Miller et al. showed a reversal of regioselectivity under similar reaction conditions by treating with functionalized alkyne bearing ester or amine groups. The best regioselectivity were observed with the carbamate containing a 2,2,2-trichloroethoxycarbonyl (Troc)submotif (equation 7).[14]



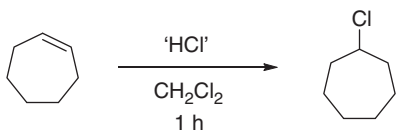
(7)

4.05.2.3 H–Cl Addition

4.05.2.3.1 Hydrochlorination of alkenes

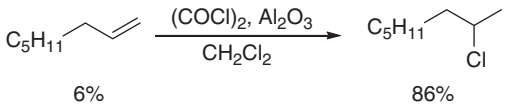
Electrophilic addition of hydrogen halides to olefins is one of the classical reactions in organic synthesis, having served as the basis for Markovnikov's well-known rule on the regioselectivity of electrophilic additions.[15] Despite numerous examples of HCl's addition to alkenes in the textbooks, it does not add to alkenes at preparatively useful rates unless they are strained,[16] highly substituted,[17] or part of a styryl system.[18] Several different experimental procedures have been developed to address this low reactivity issue.

Kropp et al. addressed this low reactivity issue by the application of surface-mediated process, which also greatly simplified the procedure.[19] For example, the hydrochlorination reaction cannot occur at all with a saturated solution of HCl in CH_2Cl_2 at room temperature, wherein 97% of olefin is recovered, whereas the desired product can be obtained in 62% yield on treatment of the solution with silica gel. The combination of other HCl precursors such as $SOCl_2$ or $(COCl)_2$ with silica gel or alumina could give higher yields (equations 8 and 9).



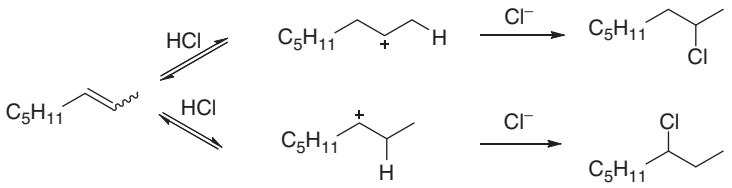
97%	HCl	0%
3%	HCl, SiO_2	62%
3%	$SOCl_2$, SiO_2	81%

(8)



(9)

This surface-mediated process is applicable to a quite general substrate scope, but rearrangements leading to side products still cannot be avoided in some cases. Thus, surface-mediated addition is believed to proceed via a stepwise process involving the carbocation intermediate. For example, the hydrochlorination of 2-octene would give 2-chlorooctane with some amount of the 3-halo isomer (equation 10). Similarly, 3,3-dimethyl-1-butene afforded a mixture of the unrearranged and rearranged chlorides; the selectivity is affected by the nature of substrate and the reaction conditions (equation 11). α-Pinene even underwent skeletal rearrangement to release the strain energy, leading to a mixture of chlorated bicyclo-[2,2,1]-heptanes (equation 12).[20] More rearrangement occurred over the silica gel-surface system than it occurred for the alumina-surface.



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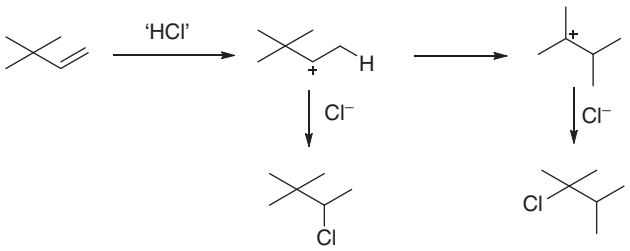
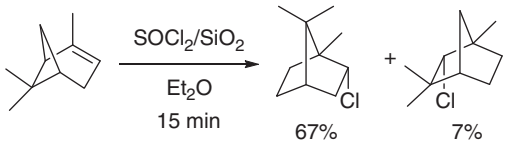


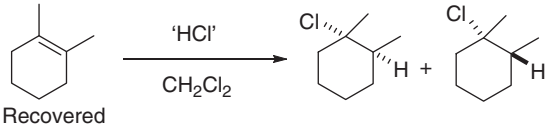
HCl/Al_2O_3, $CHCl_3$, 16 h	31	:	69
HCl/SiO_2, $CHCl_3$, 3.5 h	17	:	83
HCl/SiO_2, C_5H_{12}, 4 h	19	:	81

(11)



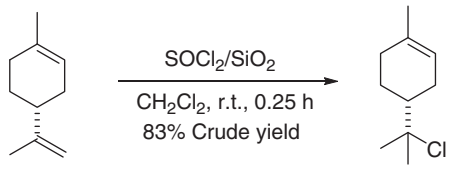
(12)

The stereochemistry of surface-mediated hydrochlorination was examined using the tetrasubstituted 1,2-dimethylcyclohexene. It was found that the hydrochlorination prefers *syn* addition (*syn*/*anti* = 5:1) of HCl in solution, whereas a thermodynamic ratio (1:3) of *syn* and *anti* addition products was obtained under the $(COCl)_2$/alumina conditions (equation 13). The authors mentioned that silica gel and alumina surfaces presumably promote ionic addition through hydrogen-bonding interactions and they both polarize the H–X bond and reduce entropy effects by bringing the two reactants together.



(13)

One double bond of the unconjugated dienes can selectively be hydrochlorinated under the surface-mediated conditions. For example, the reaction of (*R*)-limonene with 0.5 equivalent of $SOCl_2$ at room temperature in the heterogeneous media SiO_2/CH_2Cl_2 produced (*R*)-α-terpinyl chloride in good yield with a little racemization (equation 14),[21] whereas the traditional homogeneous conditions require a slow addition of dry gaseous HCl to dry limonene at low temperature and long reaction time.[22] Under similar reaction conditions, isoprene undergoes 1,4-addition to afford prenyl chloride in 82% yield (equation 15).[23]



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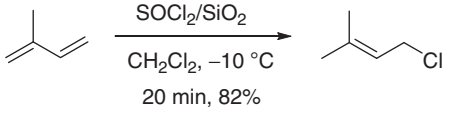
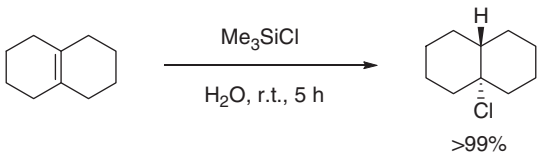


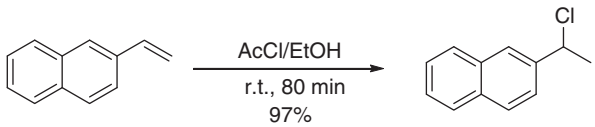
(15)

A new chemo- and regioselective hydrochlorination procedure was reported by Boudjouk et al. using a mixture of trimethylchlorosilane and water, which is applicable to a series of simple and functionalized olefins.[24] Markovnikov addition for simple olefins and *anti*-Markovnikov addition for α,β-unsaturated olefins dominate. For example, $\Delta^{9,10}$-octaline gave a *trans* product in >99% yield (equation 16).



(16)

Recently, Yadav has demonstrated an efficient Markovnikov hydrochlorination of olefins with AcCl/alcohol as the source of HCl.[25] Those olefins that generated more stable benzylic and tertiary carbocations on Markovnikov protonation would react rapidly and furnish products in higher yields. Electron-rich alkenes such as 2-vinylnaphthalene and 4-methoxystyrene underwent HCl addition faster than the less electron-rich olefins (equations 17 and 18). Addition of HCl to carvone was chemospecific as it takes place only with the more electron-rich olefin (equation 19).



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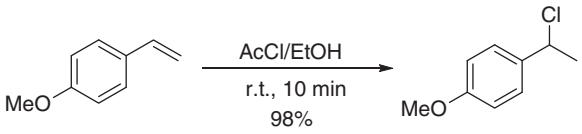

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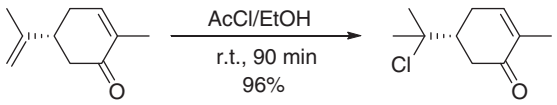
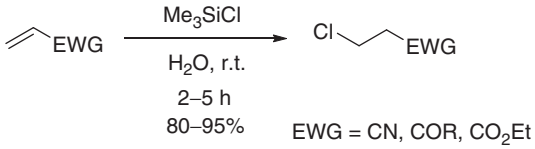


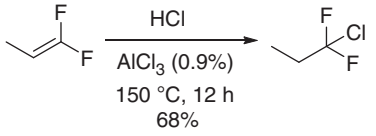
(19)

The addition of HCl to electron-deficient alkenes provided a useful approach to functionalized organic chlorides. The hydrochlorination reactions of α,β-unsaturated ketones, carboxylate, and nitriles through nucleophilic addition were accomplished using a mixture of trimethylchlorosilane and water at room temperature (equation 20).[24]



(20)

To less reactive alkenes, particularly those bearing one or more fluorine atoms, it is often advisable to add a Lewis acid catalyst such as $AlCl_3$ in order to promote the reaction (equations 21 and 22).[26]



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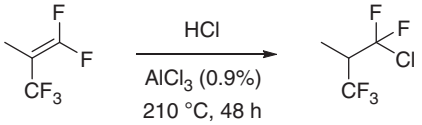
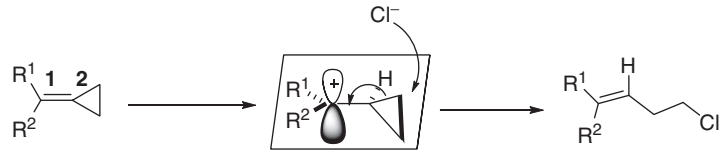


(22)

Methylenecyclopropanes (MCPs) and alkylidenecyclopropanes (ACPs) are reactive olefins because of the high strain energy. Yamamoto et al. described an efficient procedure for the synthesis of homoallylic halides. The reaction of ACPs with HCl proceeds smoothly at 120 °C in order to afford the corresponding homoallylic chloride stereoselectively in good to excellent yields (equation 23, Condition A).[27] It should be noted that unsymmetrical ACPs would generate the *E*-homoallylic chlorides stereoselectively. The protonation at the C-2 position leads to a more stable cyclopropylcarbinyl cation. If R^1 is sterically bulkier than R^2, the smaller group H is located most probably on the R^1 side of the plane and the larger group (CH_2CH_2Cl) is on the R^2 side. Shi's group later achieved a similar transformation by using LiCl and acetic acid to generate HCl *in situ*. The reaction produces *gem*-disubstituted homoallylic halides in good to excellent yields (equation 23, Conditions B).[28]



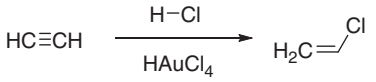
(23)

Conditions A: 4 M HCl in 1,4-dioxane or 1 M HBr in HOAc, 120 °C — $R^1 = R^2$ = Ph, Bu, Hex; R^1 = alkyl, R^2 = H, Me; 83–99%

Conditions B: LiCl (1.5 equivalents), HOAc, 80 °C — $R^1 = R^2$ = aryl, alkyl; 89–100%

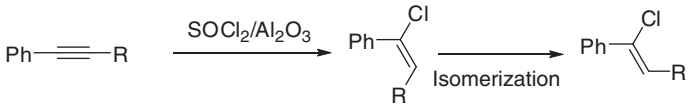
4.05.2.3.2 Hydrochlorination of alkynes

Numerous procedures, usually involving a metal chloride catalyst, have been developed for the industrially important conversion of acetylene to vinyl chloride. The addition of hydrogen chloride to acetylene, catalyzed by tetrachloroauric acid, delivers the corresponding vinyl chloride (equation 24).[29]



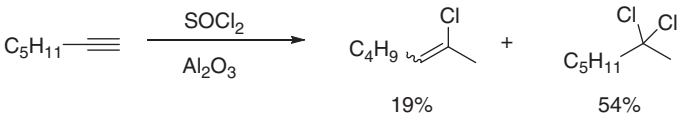
(24)

Kropp et al. applied their self-developed surface-mediated procedure to the hydrochlorination of the alkynes, which became a convenient method for the preparation of alkenyl chlorides.[30] The addition of HCl precursors to disubstituted alkynes generally produces *syn* adducts in order to give the *E*-stereoisomer, which undergoes further isomerization with longer reaction time in order to afford the thermodynamically more stable *Z*-isomer. Either isomer could be obtained in good yields by controlling the reaction time (equation 25). However, the terminal 1-heptyne afforded principally a mixture of double-bond-rearranged alkenyl chloride and *gem*-dichloride under the same conditions (equation 26).



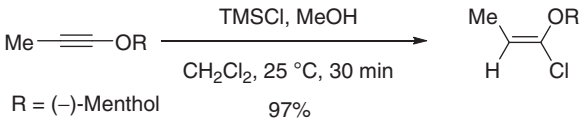
	(*E*)	(*Z*)
R = Me, 0.3 h	66%	29%
3 h	1%	82%
R = *t*-Bu, 0.3 h	99%	–
24 h	13%	44%
R = Ph, 0.3 h	66%	–
16 h	5%	77%

(25)



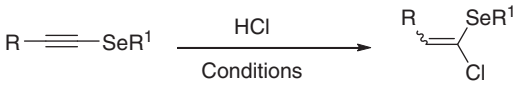
(26)

α-Halo vinyl ether can easily be prepared from alkynyl ether with HCl generated *in situ* from TMSCl and methanol (equation 27).[31] It should be noted that the reaction employing TMSCl and methanol was not only faster but also gave better stereoselectivity than that obtained while using commercially available HCl in ether.



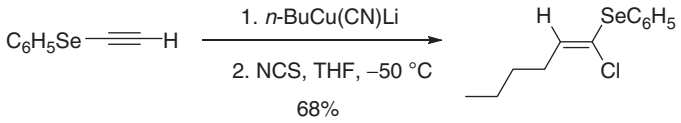
(27)

The regioselective hydrochlorination of acetylenic selenides was reported by Comasseto et al. to afford 1-halo-1-selenoalkenes in good yields, although the reaction proceeded with no stereochemical control.[32] Three hydrochlorination procedures were investigated and a mixture of two stereoisomers of 1-chlo-1-selenoalkenes with different ratio was obtained (equation 28). The authors used an alternative strategy to address this stereoselectivity issue by reacting phenylselenoacetylene with lithium butylcyanocuprate to give alkenylcyanocuprate intermediate, which was trapped by *N*-chlorosuccinimide (NCS), stereoselectively leading to *E*-trisubstituted vinylic selenide in 68% yield (equation 29).



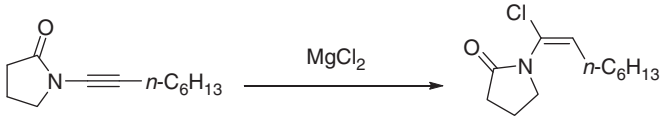
(28)

Conditions A: 37% HCl, benzene/HOAc (3:1), *Z*/*E* = 1.4:1 ~ 16.7:1
Conditions B: 37% HCl, $CHCl_3$, $HgCl_2$ (5 mol%), *Z*/*E* = 1.3:1 ~ 14.1:1
Conditions C: dry HCl saturated in benzene, *Z*/*E* = 1:1.7 ~ 16.2:1



(29)

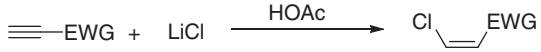
A facile highly stereoselective access to (*E*)-α-haloenamides via hydrochlorination of ynamides was achieved by Hsung et al. (equation 30).[33] The authors proposed that the source of HCl was *in situ* generated from magnesium salt and trace amount of H_2O in the reaction.



(30)

CH_3CN, 65 °C, 24 h, 71%, *E*/*Z* = 95:5
DCE, 100 °C, 24 h, 75%, *E*/*Z* = 95:5

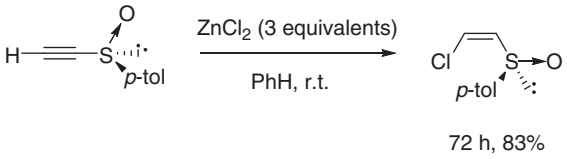
The use of metal halides in acetic acid has been long examined as a useful reaction system since Ma and Lu's pioneering work. A wide variety of 2-propynoic acid and its derivatives has been reported to react with lithium chloride in acetic acid or preferably with 1 equivalent of acetic acid in refluxing CH_3CN in order to afford the thermodynamically unfavorable (*Z*)-3-chloropenoic acids and their derivatives (equation 31).[34] The stereoselectivity and yield are significantly affected by the solvent and reaction temperature used.



EWG = CO_2R, CO_2H	CH_3CN,reflux	75–85%
$CONR^1R^2$	90 °C	36–98%
CN	70 °C	85%

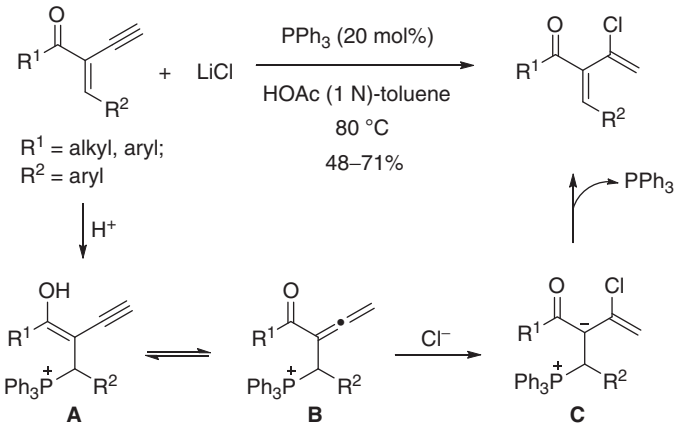
(31)

Paley et al. reported hydrochlorination reactions of enantiopure sulfinylethyne with $ZnCl_2$ in benzene. The method provides the corresponding (*Z*)-chlorides in good yields (equation 32).[35]



(32)

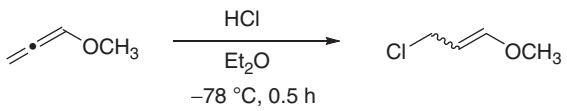
A novel Ph_3P-catalyzed regioselective hydrochlorination of electron-deficient 1,3-conjugated enynes was recently found, yielding 2-choloro-1,3-dienes as single geometrical isomers (**Scheme 5**). The reaction may undergo an allene intermediate followed by S_N2'-type reaction.



Scheme 5 PPh_3-catalyzed hydrochlorination of 1,3-conjugated enynes.

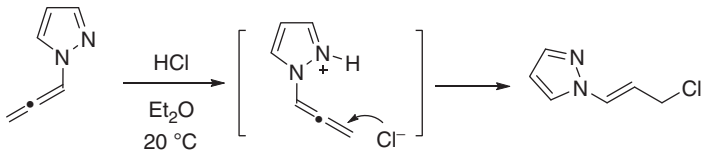
4.05.2.3.3 Hydrocholorination of allenes

Considerably more work has been reported on the addition of HCl to allenes.[36] Electron-rich allenes underwent HCl addition at the terminal double bond of the allenyl moiety. For example, a solution of gaseous HCl in dry Et_2O was added dropwise under N_2 to a solution of 1-methoxyallene in Et_2O at −78 °C in order to afford 1-chloro-4-methoxy-2-butene (equation 33). The resulting solution of 1-chloro-4-methoxy-2-butene was kept at 0–5 °C until it could be used in the next step.[37]



(33)

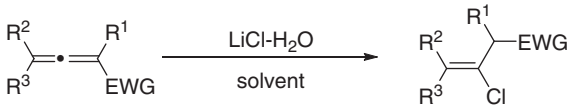
1-Allenylpyrazole reacted with hydrogen chloride via proton addition at the pyridine-like nitrogen atom (equation 34).[38] 1-[(*E*)-3-chloro-1-propenyl]pyrazole was obtained via addition of HCl at the terminal double bond of the allenyl moiety, which can be transformed into a viscous polymeric adduct.



(34)

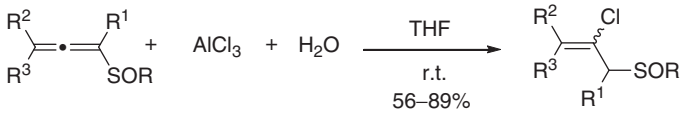
Ma et al. have done a comprehensive study on hydrochlorination reaction of various electron-deficient allenes,[39] such as 1,2-allenic ketones, carboxylic acids, esters, amide, nitriles, sulfones, and phosphine oxides, with MX (M = Na and Li) in HOAc, CF_3CO_2H–HOAc, CF_3CO_2H, or tetrahydrofuran (THF), affording 1-functionalized 2-halo-2-alkenes with high β,γ-selectivity over α,β-selectivity (**Scheme 6**).[40] This hydrohalogenation reaction is a nucleophilic conjugate addition in nature.

The reaction of 1,2-allenic sulfoxides with MCl in HOAc failed to give the expected 2-haloallylic sulfoxides. A novel reaction system $AlCl_3/H_2O$ was developed to solve this problem (equation 35).[41] A mechanism for this hydrochlorination reaction involves the Al(III)-mediated nucleophlic attack of X^- at the center carbon atom of the electron-deficient allenes.



EWG	Solvent	T (°C)	Yield (%)
COMe	HOAc or CF_3CO_2H-HOAc	25	70–90
CO_2H	HOAc	reflux	87
CO_2Et	HOAc or CF_3CO_2H	80 or reflux	63–84
CN	HOAc or CF_3CO_2H-HOAc	70	76–80
CONHR	HOAc	70	75–99
SO_2R	HOAc	80 or reflux	67–80
$POPh_2$	HOAc	100	58–75

Scheme 6 Hydrochlorination of electron-deficient allenes.



R = Ph, CH_3
R^1 = H, CH_3
R^2 = H, CH_3
R^3 = H, CH_3

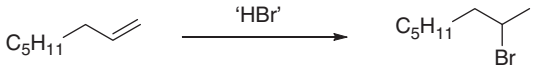
(35)

4.05.2.4 H–Br Addition

4.05.2.4.1 Hydrobromination of alkenes

HBr is ready to add to most olefins. However, a competing radical chain addition producing the *anti*-Markovnikov product is often accompanied unless they are highly substituted or part of a styryl system. This competing reaction in some cases predominates and thus stringent precautions are necessary to take in order to overcome this issue.[42]

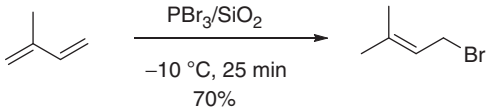
Surface-mediated addition is a simple strategy to prevent competing radical process. Treatment with $(COBr)_2$ or $(CH_3)_3SiBr$ as HBr precursors at −78 °C, 1-octene rapidly affords the ionic addition product in the presence of silica gel or alumina (equation 36).[20]



HBr/SiO_2	0.7 h, 96%
HBr/Al_2O_3	0.3 h, 93%
$(COBr)_2/Al_2O_3$	0.3 h, 99%
$(CH_3)_3SiBr/Al_2O_3$	2 h, 99%

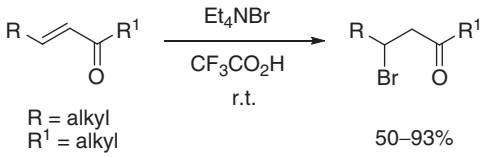
(36)

The silica-mediated hydrobromination of limonene with PBr_3/SiO_2 proceeds smoothly to produce the corresponding α-terpinyl halides. This silica-mediated procedure is applicable to a variety of alkenes.[43] The 1,3-diene isoprene with PBr_3/SiO_2 underwent exclusively 1,4-addition to afford prenyl bromide (equation 37).[23]



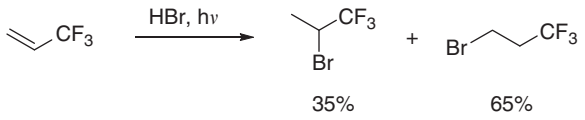
(37)

The hydrobromination of a number of electron-deficient olefins has also been extensively studied. Mark reported a simple procedure for synthesis of β-bromo-ketones in the presence of a tetraalkyl ammonium bromide in anhydrous trifluoro acetic acid (equation 38).[44]



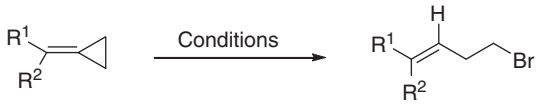
(38)

The addition of HBr to 3,3,3-trifluoro-1-propene was carried out under photochemical conditions to give a mixture of 2-bromo-3,3,3-trifluoropropane (35%) and the desired 1-bromo-3,3,3-trifluoropropane (65%) (equation 39).[45]



(39)

Similar to the hydrochlorination case, the reaction of symmetrical MCPs with 1 M hydrogen bromide at 120 °C in acetic acid gave the corresponding homoallylic bromide in 95% yield (equation 40, Conditions A).[27] Again, this hydrobromination can be accomplished by the use of LiBr and acetic acid as hydrohalogenating reagents (equation 40, Conditions B).[28]



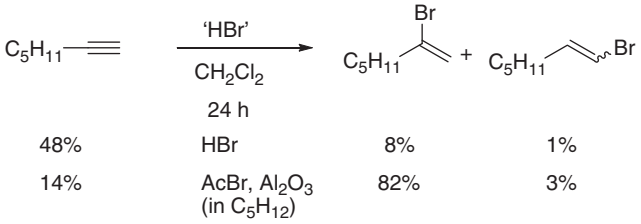
(40)

Conditions A: HBr (1.1 equivalents), HOAc, 120 °C $R^1 = R^2$ = Bu, 95%

Conditions B: $LiBr{\cdot}H_2O$ (1.5 equivalents), HOAc, 80 °C $R^1 = R^2$ = Aryl, alkyl 80–100%

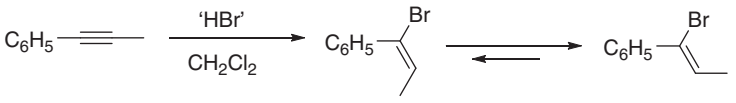
4.05.2.4.2 Hydrobromination of alkynes

The terminal aliphatic alkyne underwent slow addition of HBr in solution, leading to the alkenyl products in very low yields, whereas good yields and better regioselectivity could be obtained under the alternative conditions: AcBr over alumina (equation 41).[19]



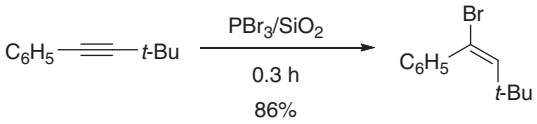
(41)

1-Phenylpropyne reacted rapidly with a saturated solution of HBr in CH_2Cl_2 but afforded a mixture of the corresponding bromides and the radical products (anti-Markonikov products) as the major products. In contrast, this radical process can be well suppressed by using the surface-mediated procedure, giving (*E*)-alkenyl bromide in high yield (equation 42). In the presence of excess reagent, it rapidly converted into the thermodynamically more stable *Z*-isomer. Either isomer could be obtained in good yield by proper choice of reaction conditions. Similarly, treatment of the *tert*-butyl analog with PBr_3 over silica gel for short times afforded the *syn* adducts in 86% yield (equation 43).[30]



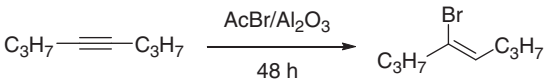
0%	HBr, 3 h	29%	8%
0%	HBr, Al_2O_3, 0.3 h	14%	79%
2%	PBr_3, Al_2O_3, 3 h	82%	10%
0%	PBr_3 (xs), Al_2O_3, 3 h	4%	80%

(42)



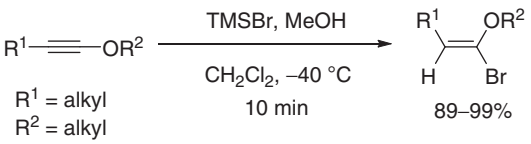
(43)

This surface-mediated procedure is also applicable to the internal alkylalkyne. For example, the reaction of 4-octyne with AcBr over alumina afforded principally the *anti* addition product in 72% yield after 48 h (equation 44).[30]



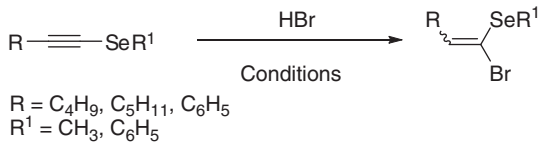
(44)

Similar to hydrochlorination reaction, a highly regio- and stereoselective method for the synthesis of (*E*)-α-bromo vinyl ethers using HBr generated *in situ* from TMSBr and methanol has been reported by Jin et al. (equation 45).[31] The yield was nearly quantitative and column chromatography for purification was necessary.



(45)

It was found that hydrobromination of acetylenic selenides could take place at room temperature, leading to 1-bromo-1-selenoalkenes regiospecifically in good yields with up to 14.7:1 *E*:*Z* ratio (equation 46).[32]

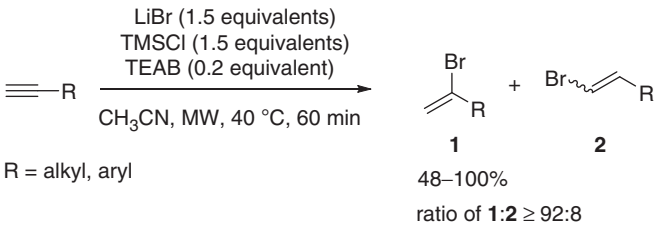


$R = C_4H_9, C_5H_{11}, C_6H_5$
$R^1 = CH_3, C_6H_5$

(46)

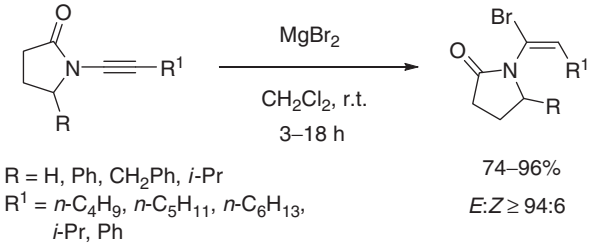
Conditions A: 48% HBr, benzene/HOAc (3:1)	*E*/*Z* = 4.8:1 ~ 10.8:1; 74–84%
Conditions B: 48% HBr, $CHCl_3$, $HgCl_2$ (5 mol%)	*E*/*Z* = 5.9:1 ~ 14.1:1; 75–82%
Conditions C: dry HBr saturated in benzene	*E*/*Z* = 1:2.1 ~ 14.7:1; 72–83%

Recently, a combination of LiBr, TMSCl, and TEAB in acetonitrile was found to be an efficient procedure for hydrobromination of terminal alkynes under microwave irradiation conditions, as evidenced by the corresponding 2-bromo-1-alkenes obtained in good yields regioselectivity (equation 47).[46]



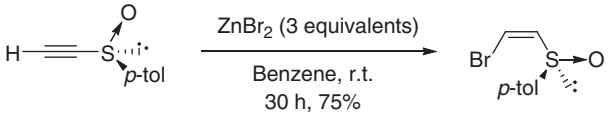
(47)

The hydrobromination of ynamides at ambient or moderate temperature for the synthesis of (*E*)-α-bromoenamides was explored by Hsung et al. with the use of magnesium salts in wet solvents (equation 48).[33] This transformation is regiospecific without the detection of β-bromoenamide regioisomer.



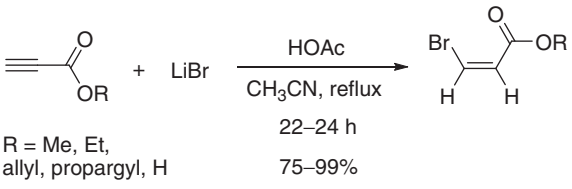
(48)

Paley et al. applied 3 equivalents of $ZnBr_2$ to the hydrobromination of enantiopure sulfinylethyne in benzene, leading to the desired adduct (*Z*)-2-bromo vinyl sulfoxide in 75% yield after 30 h (equation 49).[35] The coordination of halogenated Lewis acid to the sulfinyl oxygen might help delivering a halide in a stereospecific manner to an alkynyl sulfoxide.

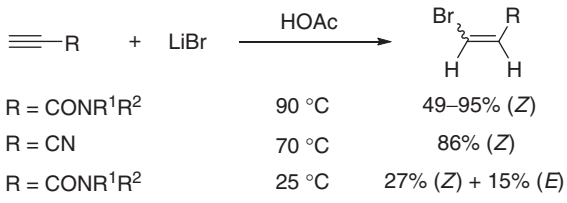


(49)

2-Propynoic acid and its derivatives were smoothly converted into the corresponding (*Z*)-3-bromopropenoic acid and its derivatives as sole products with lithium bromide in acetic acid or preferably with 1 equivalent of acetic acid in refluxing CH_3CN (equation 50).[34] This hydrobromination procedure was also applicable to 2-propynamide, 2-propynenitrile, and 1-phenyl-2-propynone in good yields (equation 51).

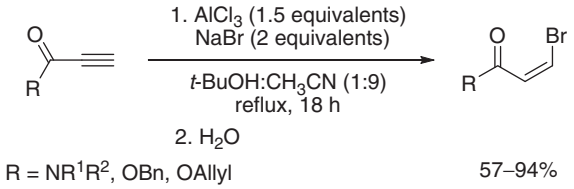


(50)



(51)

Feray et al. found that $AlCl_3$–NaBr–*t*-BuOH system in refluxing acetonitrile could promote the hydrobromination of 2-propynamides and propynoic esters to produce (*Z*)-bromo-propenamides and corresponding esters in moderate to good yields (equation 52).[47] However, (*E*)-2-bromovinyl phenyl ketones as a single isomer was obtained in 69% yield when applying this hydrobromination procedure to phenylpropynone (equation 53).



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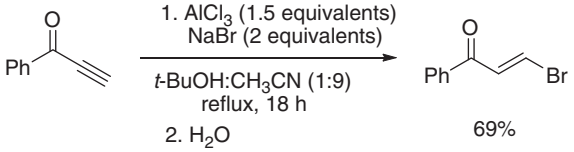
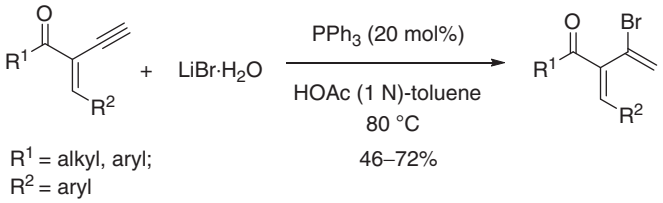


(53)

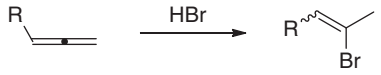
The Ph_3P-promoted hydrobromination reaction of 2-(1-ethynyl)-2-alken-1-ones using metal bromides in HOAc (1 N)-toluene solvent at 80 °C could give the corresponding vinyl bromides in moderate yields (equation 54).



(54)

4.05.2.4.3 Hydrobromination of allenes

In earlier reports, the addition of HBr to terminal monosubstituted allenes afforded primarily (*E*)- and (*Z*)-2-bromo-2-alkenes using HBr in either solvent or gas phase (equation 55).[48] However, terminal disubstituted allenes gave different regioisomers (equation 56).[48a,b]



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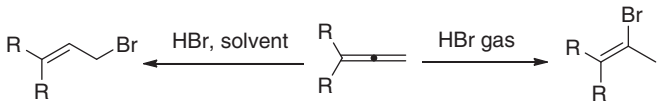
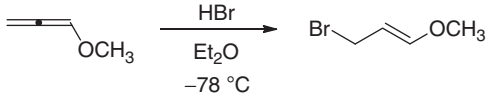


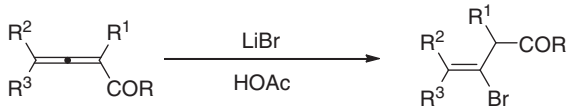
(56)

Hagen et al. also found that the hydrobromination of 1-methoxyallene takes place at the terminal double bond, leading to 3-bromo-1-methoxypropene at low temperature (equation 57).[49]



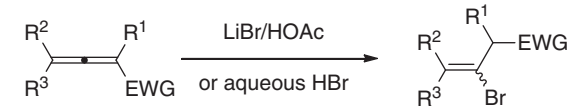
(57)

Besides the hydrochlorination, Ma et al. have also done seminal contribution in the field of hydrohalogenation of electron-deficient allenes. 1-Functionalized 2-bromo-2-alkenes were easily synthesized by the regioselective hydrobromination of the corresponding electron-deficient allenes (equations 58 and 59).[39,40,50] Although the stereoselectivity is not high in many cases, the *Z*- and *E*-isomers can easily be separated by chromatography on silica gel.



$R^1 = R^3 = R = H$, $R^2 = n\text{-}C_4H_9$	89%, *Z*/*E* = 70:30
$R^1 = R^3 = R = H$, $R^2 = n\text{-}C_7H_{15}$	82%, *Z*/*E* = 64:36
$R^2 = R^3 = R = H$, $R^1 = Me$	61%
$R^1 = R^3 = H$, $R^2 = Me$, R = OEt	83%, *Z*/*E* = 5.5:1
$R^1 = R^3 = H$, $R^2 = n\text{-}C_6H_{13}$, R = OEt	72%, *Z*/*E* = 1:1

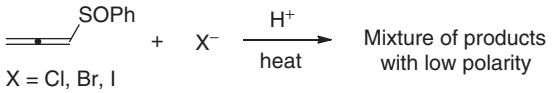
(58)



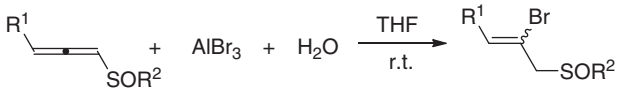
R^1 = H, Me
R^2 = H, Me, *n*-Bu, Ph
R^3 = H, Me
EWG = CN, CONHR, SO_2R, $POPh_2$

58–98% (59)

However, this procedure cannot be applied to 1,2-allenic sulfoxides, which failed to provide the expected 2-haloallylic sulfoxides (equation 60).[40] Ma et al. addressed this issue by using an alternative HBr precursor, for example, $AlBr_3$ and H_2O, leading to the desired conjugate addition product (equation 61).[41]



(60)



R^1 = H, CH_3, *n*-C_4H_9
R^2 = CH_3, Ph

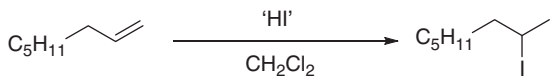
56–89% (61)

4.05.2.5 H–I Addition

4.05.2.5.1 Hydroiodination of alkenes

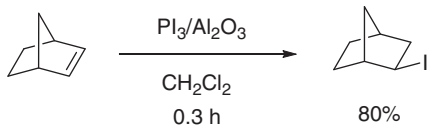
The addition of HI to alkenes and alkynes is faster than that of the other hydrohalides, in which the free-radical *anti*-Markovnikov addition is not a problem anymore. Several alternative approaches to hydroiodination have been developed in the past years.

The treatment of 1-octene with PI_3 as an HI precursor in the presence of silica gel or alumina could afford the corresponding alkyl iodide in good yield (equation 62).[19] This method was found to be also effective for the hydroiodination of 2-norbornene to produce the desired alkyl iodide in 80% yield (equation 63).[20]



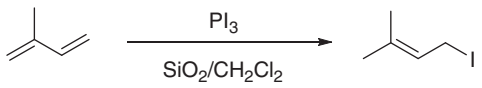
4% PI_3/SiO_2, 0.3 h 78%

9% PI_3/Al_2O_3, 0.3 h 91% (62)



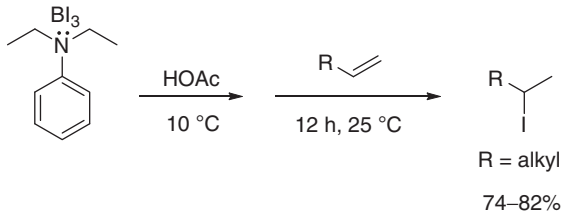
80% (63)

De Mattos et al. extended this surface procedure to the hydroiodination of 1,3-dienes such as isoprene. The hydroiodination reaction was performed at −10 °C in an open flask, leading to 65% yield of prenyl iodide (equation 64).[23]



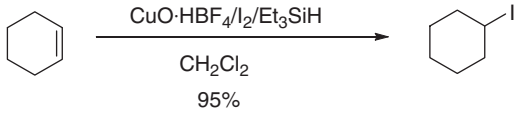
(64)

Periasamy et al. found that BI_3/*N*,*N*-diethylaniline complex and acetic acid is another efficient combination for hydroiodination of unreactive alkenes in Markovnikov fashion under mild conditions (equation 65).[51]

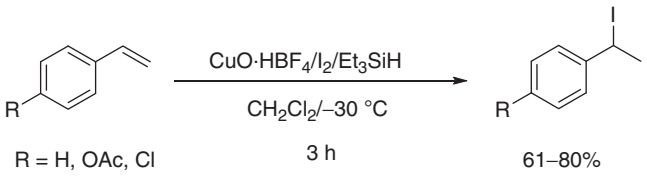


(65)

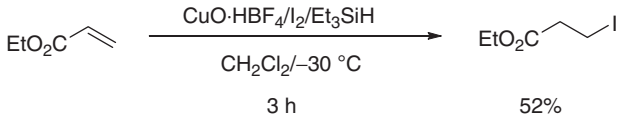
The reagent system $CuO{\cdot}HBF_4/I_2/Et_3SiH$ generated hydrogen iodide *in situ*, which added regioselectively to alkenes. The hydroiodination of cyclohexene afforded iodocyclohexane in excellent yield (equation 66).[52] Various functional groups such as acetal are tolerated to give the Markovnikov adducts (equation 67). This reaction procedure is also applicable to electron-deficient alkenes, for example, the reaction of ethyl acrylate under the same experimental conditions gave ethyl 3-iodopropionate in moderate yield (equation 68).



(66)

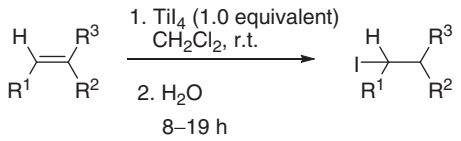


(67)



(68)

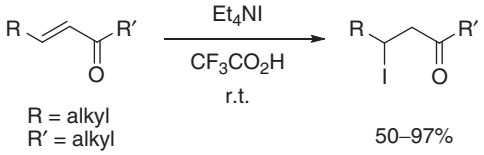
Shimizu et al. demonstrated that TiI_4 is an efficient reagent for hydroiodination of different electron-nature of olefins. For example, a variety of olefins react smoothly with one equivalent of titanium tetraiodide in CH_2Cl_2 at room temperature to afford the secondary iodinated products in moderate yields (equation 69).[53]



$R^1 = R^2 = -(CH_2)_n-$, $R^3 = H$	51–91%
$R^1 = R^2 = i\text{-}PrO_2C$, $R^3 = H$	34%
$R^1 = R^3 = C_5H_{11}$, $R^2 = H$	54%
$R^1 = Ph(CH_2)_2$, Ph, $R^2 = R^3 = H$	53–78%

(69)

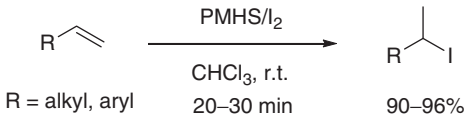
Mark et al. found that tetraalkyl ammonium iodide react with α,β-unsaturated enones in trifluoroacetic acid at room temperature to produce β-iodoketones as the only detectable product (equation 70).[44]



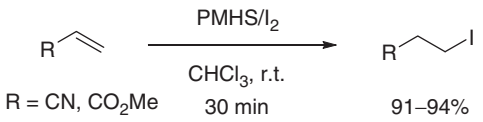
(70)

Using polymethylhydrosiloxane (PMHS) and iodine as reagents in chloroform at room temperature, Das et al. developed another protocol for hydroiodination of alkenes.[54] The reaction has a general substrate scope, and the unsysmmetric substituted

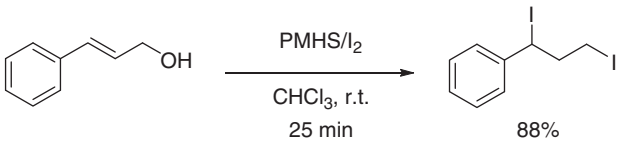
alkenes regioselectively afforded a single regioisomer following Markovnikov's rule (equation 71). However, methyl acrylate and -acrylonitrile yielded methyl-3-iodopropanoate and 3-iodopropanenitrile via Michael addition (equation 72). Under these reaction conditions, the alcohol would also undergo iodination via substitution, for example, the reaction of cinnamyl alcohol would afford 1,3-diiodopropyl benzene in 88% yield via the substitution and addition process (equation 73).



(71)

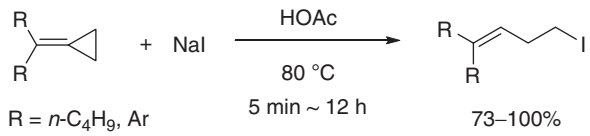


(72)



(73)

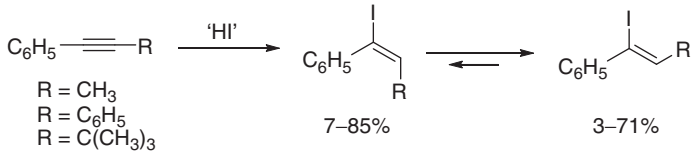
Owing to high strain energy, the hydroiodination reactions of MCPs with NaI in acetic acid at 80 °C proceed smoothly to produce the corresponding *gem*-disubstituted homoallylic iodides in good yields (equation 74).[28] It was proposed that the rearrangement of cyclopropyl carbinyl cation to a homoallylic cation induced by acetic acid was the key step for the ring-opening reaction.



(74)

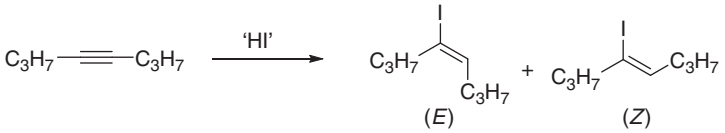
4.05.2.5.2 Hydroiodination of alkyne

The addition of HI to electron-rich alkynes reacted slowly in solution, affording a mixture of (*E*)- and (*Z*)-iodides. This issue can be well addressed by running the reaction over silica gel or alumina using acetyl iodide or PI_3 as an HI precursor. The *syn* adduct (*E*)-iodide was initially formed preferentially, whereas at longer time, *E*↔*Z* isomerization afforded the more stable (*Z*)-isomer (equation 75). Surface-mediated addition of HI to the internal alkylalkyne afforded principally (*Z*)-iodide, accompanied by some amount of the *E*-isomer (equation 76).[30]



'HI': AcI/SiO_2 or Al_2O_3; PI_3/SiO_2 or Al_2O_3

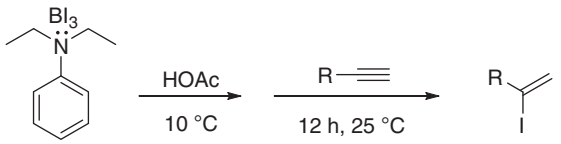
(75)



HI	24 h		78%
AcI/SiO_2	0.3 h	21%	60%
AcI/Al_2O_3	1 h	16%	62%
AcI/Al_2O_3	24 h	18%	77%

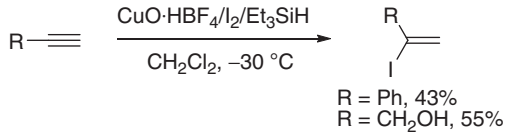
(76)

The hydroiodination reactions of terminal alkynes can also be achieved by using BI_3/*N*,*N*-diethylaniline complex in the presence of acetic acid at room temperature, leading to Markovnikov adducts in good yields (equation 77).[51]

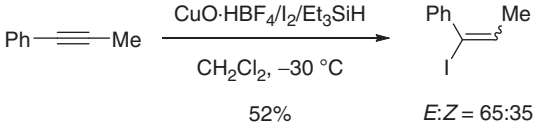


(77)

When the CuO·HBF_4/I_2/Et_3SiH system was used, the hydroiodination reactions of alkynes proceeded smoothly. A monohydroiodination of phenylacetylene was observed to produce α-iodostyrene in 43% yield (equation 78). In a similar reaction, 1-phenyl-1-propyne gave a mixture of 1-iodo-1-phenyl-1-propene in 52% yield with *E*/*Z* ratio of 65:35 (equation 79).[52]

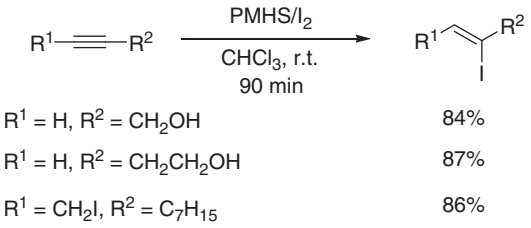


(78)



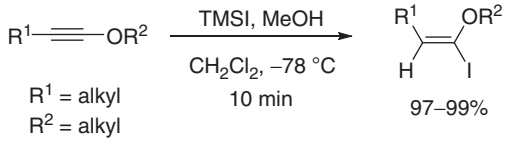
(79)

Using PMHS–I_2 reagents at room temperature, the direct hydroiodination of functionalized alkynes was realized to afford alkenyl iodides in high yields under mild conditions, which obeyed Markovnikov rule (equation 80).[53]



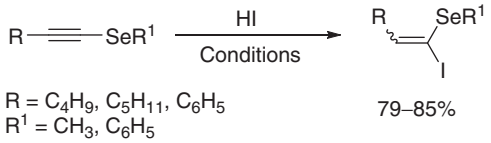
(80)

Acetylenic ethers also undergo hydroiodination on reaction with trimethylsilyl (TMS) iodide and MeOH in CH_2Cl_2 at low temperature to give good yields of α-iodo vinyl ethers in a regio- and stereospecific manner (equation 81).[31]



(81)

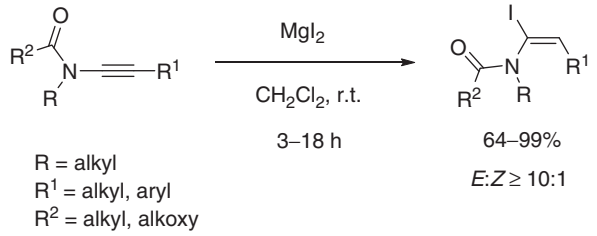
Comasseto et al. reported the addition reaction of hydrogen iodide to acetylenic selenides at room temperature to give a mixture of (*Z*)- and (*E*)-1-iodo-1-selenoalkenes in good yields; the iodide is regioselectively located at the carbon connecting with selenides (equation 82).[32]



(82)

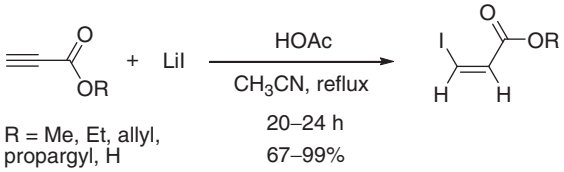
Conditions A: 51% HI, benzene/HOAc (3:1) *E*/*Z* = 1.4:1 ~ 13.2:1
Conditions B: 51% HI, $CHCl_3$, $HgCl_2$ (5 mol%) *E*/*Z* = 1.3:1 ~ 10.5:1

Similar to hydrobromination, Hsung et al. applied magnesium iodides in wet solvent for efficient hydroiodination reaction of ynamides, which led to (*E*)-α-iodoenamides in moderate to excellent yields with high *E*/*Z* stereoselectivity (equation 83).[33]



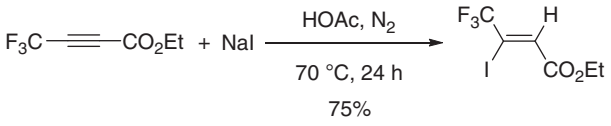
(83)

Lu et al. achieved the highly stereoselective hydroiodination reaction of 2-propynoic acid along with other 2-propynoic acid dericatives.[34] The addition of lithium iodide in acetic acid to the reaction mixture gave (*Z*)-3-iodopropenoic acids and their derivatives with excellent stereoselectivity (equation 84). The regiospecific attack of iodine ion at C-3 carbon atom of the electron-deficient carbon–carbon triple bond indicates a nucleophilic addition mechanism.



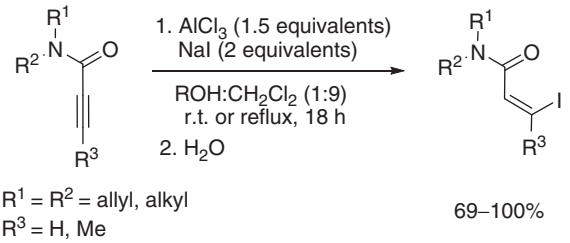
(84)

Qing et al. also found this NaI–HOAc system can be well applied to ethyl 4,4,4-trifluorobut-2-ynoate to afford (*Z*)-ethyl 4,4,4-trifluoro-3-iodobut-2-enoate as sole product in 75% isolated yield (equation 85).[55]

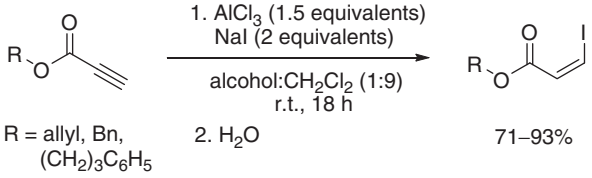


(85)

The efficiency of hydroiodination of 2-propynamides was improved by using $AlCl_3$–NaI–ROH ternary system in CH_2Cl_2 at room temperature. The reaction is stereoselective and leads to the formation of (*Z*)-iodopropenamides in high yields (equation 86).[47] Hydroiodination of nonterminal alkyne led to (*Z*)-3-iodobut-2-enamide in 69% yield after refluxing for 18 h. This method has been applied for the synthesis of vinyl iodides from propynoic esters (equation 87).

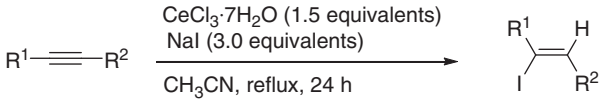


(86)



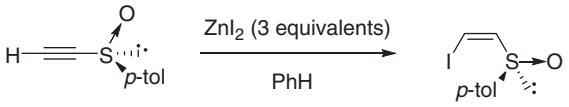
(87)

Recently, the use of $CeCl_3 \cdot 7H_2O$–NaI system as an efficient heterogeneous promoter has been highlighted in the iodo-functionalization of carbon–carbon triple bonds. The methodology tolerated alkyl-, aryl-, and heteroaryl substituents on the alkyne moiety, and in the case of internal alkynes, the hydroiodination proceeded in a highly stereoselective manner, with preferential formation of the thermodynamically more stable (*Z*)-alkenyl iodides (equation 88).[56] The reaction was initiated by coordination of Ce(III) to the triple bond, giving an organocerium intermediate by the nucleophilic attack of iodide anion, which followed by rapid protodemetalation to afford the products.

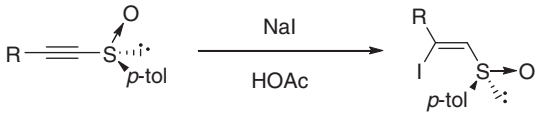


R^1 = aryl, R^2 = H, CH_3, $CH(CH_3)_2$;
R^1 = H, R^2 = CO_2CH_3;
R^1 = Ph, R^2 = $COCH_3$;
R^1 = CH_3, R^2 = CH_2OCOPh (88)

Treating enantiopure sulfinylethyne with 3 equivalents of ZnI_2 in THF provided the corresponding (*Z*)-2-iodo vinyl sulfoxide in 87% yield (equation 89). A variety of substituted sulfinylethyne reacted with NaI in HOAc via *trans*-addition to afford (*Z*)-2-iodovinyl sulfoxide in good yields (equation 90).[35]

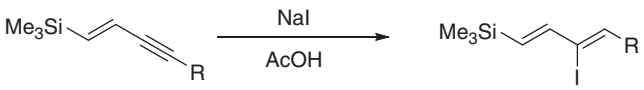


(89)



R = Bu, 82%
R = Ph, 79% (90)

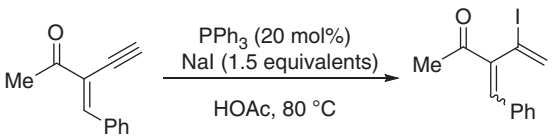
The NaI–AcOH system is also ready to highly efficient and selective hydroiodonation of conjugated enynes with electron-deficient groups, leading to the iododienamide and iododienenitrile (equation 91).[57] The TMS group is tolerated under the acidic reaction conditions.



R = $CONH_2$
R = CN

R = $CONH_2$ (54%)
R = CN (89%) (91)

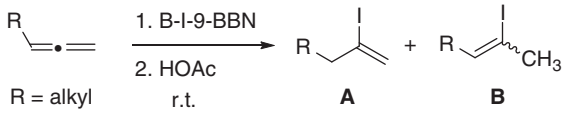
The authors also observed that 3-benzylidenepent-4-yn-2-one reacted smoothly with NaI to afford the corresponding 3-benzylidene-4-iodopent-4-en-2-one in 69% yield as a 12.5:1 mixture of *Z*- and *E*-isomers (equation 92).



(92)

4.05.2.5.3 Hydroiodination of allenes

Relatively little work has been reported on the addition of HI to electron-rich allenes. Terminal allenes reacted smoothly with B-iodo-9-borabicyclo[3.3.1]nonane (B-iodo-9-BBN), and the subsequent protonolysis with acetic acid gave the corresponding 2-iodoalkenes (equation 93).[58]

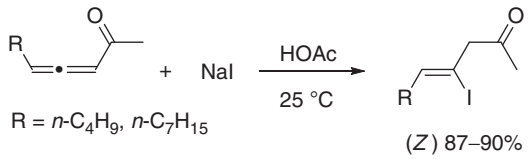


R = alkyl

55–76%

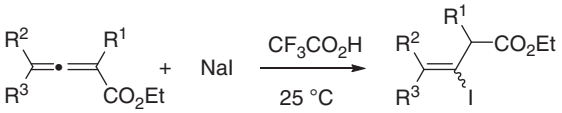
A:**B** = 56:44 ~ 94:6 (93)

Ma et al. developed the hydroiodination reaction of various types of electron-deficient allenes such as 1,2-allenic ketones, carboxylic acids, esters, amides, nitriles, sulfones, and phosphine oxides with NaI in HOAc, CF_3COOH–HOAc, CF_3COOH, or THF to afford 1-functionalized 2-iodo-2-alkenes (equations 94–97).[39,40] In most cases, the yields are high, but the stereoselectivity depends on the reaction conditions. Nucleophilic conjugate addition is believed to be a key step in these transformations.



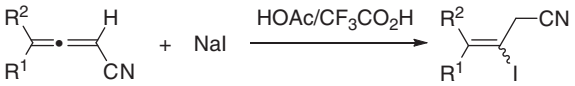
R = *n*-C_4H_9, *n*-C_7H_{15}

(*Z*) 87–90% (94)



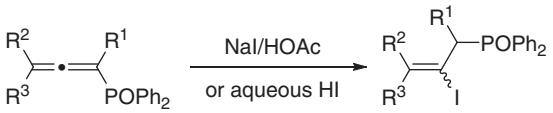
R^1 = H, Me
R^2 = H, Me, *n*-C_6H_{13}
R^3 = H, Me

55–89% (95)



R^1 = H, Me
R^2 = H, Me, *n*-Bu, Ph

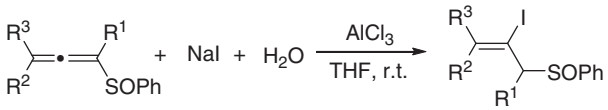
37–82% (96)



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

58–75% (97)

Hydroiodination of 1,2-allenic sulfoxides can be well addressed by using a combination of $AlCl_3$ and NaI. When 1 equivalent of 1,2-allenic sulfoxide, 1 equivalent of NaI, and 0.55 equivalent of $AlCl_3$ were used, the hydroiodination product 2-iodoallyl sulfoxide was formed in good yields together with some amount of hydrochlorination product (equation 98).[41]



$R^1 = R^2 = R^3 = H$
$R^1 = R^2 = H$, $R^3 = CH_3$

4 h, yield: 79%
3 h, yield: 69%
Z/*E* = 92/8 (98)

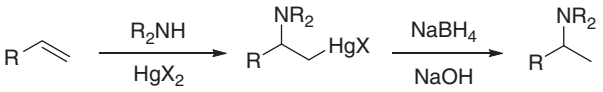
4.05.3 H–N Addition

4.05.3.1 Introduction

The addition of an amine or amine equivalent to an unsaturated carbon fragment (alkene, alkyne, or allene) has seen much progress in the past few years. Recently developed methodologies include the use of early and late transition metals.[59–62] In view of the scope of this chapter, metal-catalyzed hydroamination except aminomercuration will not be covered. The direct conjugated addition of a nitrogen-based nucleophile to α,β-unsaturated carbonyl compounds is one of the most direct and classical synthetic methods to give rise to β-amino carbonyl compounds.[63] Despite their importance and synthetic usefulness, this section would not include the progress in order to avoid the overlap with related chapters. This chapter will focus only on the progress of amino-mercuration–demercuration, hydroamination under acid catalysis, Ritter reaction, and hydroazidation.

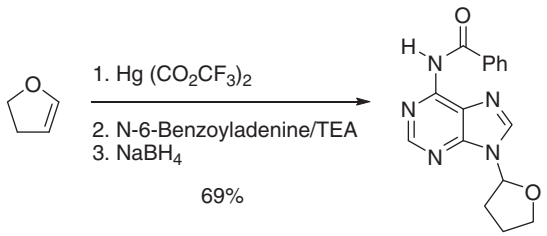
4.05.3.2 Aminomercuration–Demercuration

Aminomercuration–demercuration affords a very useful process for electrophilic addition of amines across C–C double or triple bonds. Various alkenes bearing different functional groups such as alcohol, ester, carboxylic acid, amide, imide, urea, urethane, ether, sulfide, and aryl groups have been shown to undergo aminomercuration–demercuration (equation 99).[64]



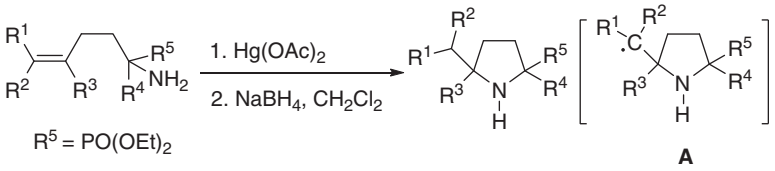
(99)

Aminomercuration of electron-rich alkenes provided a useful route to adenosine nucleoside analogs. The aminomercuration of 2,3-dihydrofuran with *N*-6-benzoyl adenine in dry THF in the presence of $Hg(O_2CCF_3)_2$ and triethylamine proceeded at 40 °C for 45 mins to afford the organomercurial intermediate, which on subsequent reduction gave the adenosine analog in 69% isolated yield as one regioisomer (equation 100).[65] Electron-rich alkenes generate more stable intermediates, leading to efficient trapping and higher yield. Unactivated alkenes such as 1-hexene and styrene were unsuccessful in the reaction.



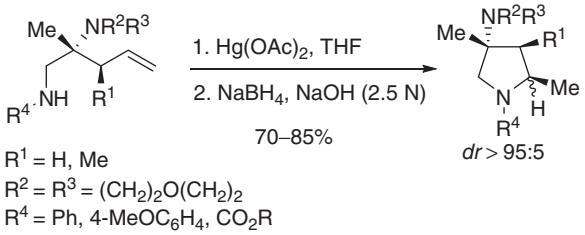
(100)

Intramolecular hydroaminations have been extensively applied to the synthesis of simple *N*-containing heterocycles such as substituted pyrrolidines and piperidines and their heteroatom-substituted analogs. The cyclization of unsaturated primary amines reported in the literature involved either an electrophilic activation of the double bond or an intramolecular addition of an aminyl radical.[66] Tordo et al. reported a complete cyclization of primary alkenylamines without recovery of the starting material (equation 101).[67] In this procedure, two moles of sodium borohydride were added to one mole of the intermediate organomercurial in order to favor hydrogen transfer to the carbon-centered radical **A** and inhibit ring opening through a β-scission process.



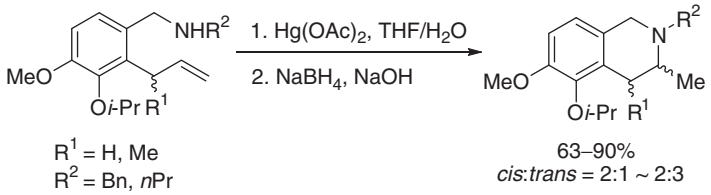
(101)

Using the electrophile-mediated cyclization methods, Barluenga et al. developed a mercuric ion-induced intramolecular cyclization of 2-amino-4-alkenylamine derivatives to prepare the corresponding 3-aminopyrrolidine derivatives in good yields with high stereoselectivity (equation 102).[68]

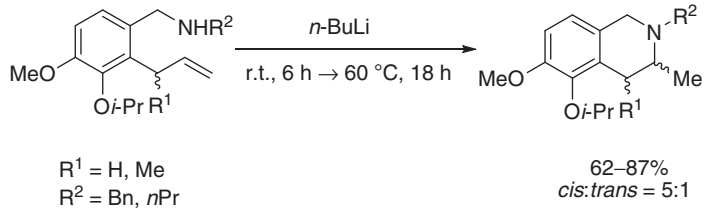


(102)

Polysubstituted tetrahydroisoquinolines were also synthesized by the mercury-mediated reductive amidation of compounds.[69] The *ortho*-allylated benzylamines were treated with a stoichiometric amount of mercury(II) acetate in a water/THF (1:1) solvent mixture (equation 103).[70] Sodium borohydride reduction of the *in situ*-formed organomercury intermediate under basic conditions led to formation of the corresponding tetrahydroisoquinolines in 63–90% yields with moderate diastereoselectivity. The reaction can also be achieved by utilizing the *n*-butyllithium-mediated approach (equation 104). The process involves an isomerization of the allyl group to the thermodynamically more stable styrene followed by the intramolecular transamination.

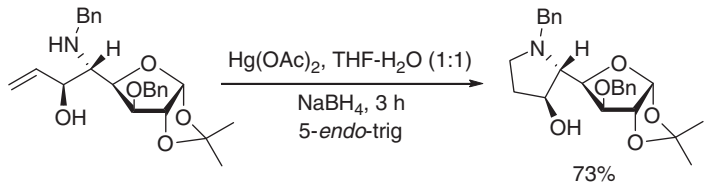


(103)



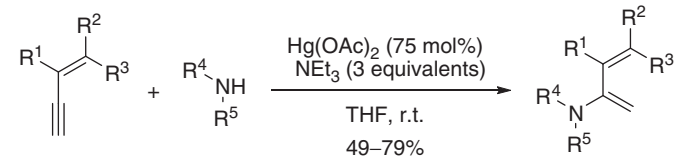
(104)

There are a few reports known on the mercury-mediated 5-*endo*-trig cyclization of γ-alkenylamine leading to the formation of a pyrrolidine ring. Dhavale et al. described that the intramolecular aminomercuration reaction of sugar-derived β-hydroxy-γ-alkenylamine underwent 5-*endo*-trig cyclization in 73% yield (equation 105).[71]

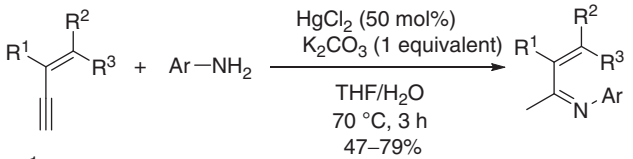


(105)

The aminomercuration of terminal carbon–carbon triple bonds led to enamines and imines. The catalytic aminomercuration reaction of 1,3-enynes with primary and secondary aliphatic and aromatic amines represents a general route to 2-amino-1,3-butadienes and 1-aza-1,3-butadienes (equations 106 and 107).[72] These compounds must be handled and stored under an inert atmosphere with exclusion of air and moisture. Otherwise, hydrolysis will occur to afford α,β-unsaturated ketones.



(106)

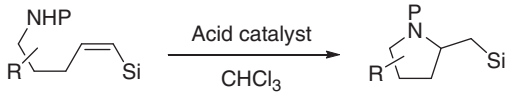


(107)

Besides these catalysts, hydroamination of alkynes can also be promoted by a base. For example, tetrabutylammonium fluoride (TBAF) has been used to synthesize five- and six-membered heterocycles via 5-*exo*-dig and 6-*endo*-dig intramolecular hydroamination of alkynes.[73]

4.05.3.3 Brønsted Acid-Catalyzed Hydroamination

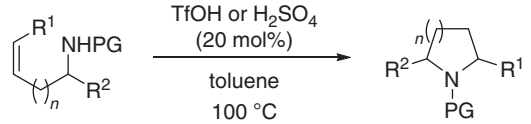
Hydroamination of unreactive olefins had been considered one of the most challenging tasks before 2000. Much progress have been made in this field by exploring new transition metals, Lewis acid, and Brønsted Acid over the past years. Hosomi et al. have reported the intramolecular hydroamination of vinylsilanes with sulfonamides to synthesize substituted pyrrolidines under the catalysis of Lewis acid or Brønsted Acid (equation 108).[74]



(108)

Condition A: $TiCl_4$, r.t.; Condition B: $TsOH{\cdot}H_2O$, at 60 °C

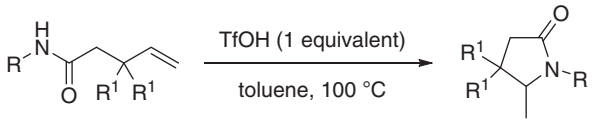
Hartwig et al. described the intramolecular hydroamination of unactive olefins with active amide under the subcatalytic amount of triflic or sulfuric acid in toluene (equation 109).[75] Pyrrolidines and piperidines were formed in excellent yields. *N*-Phenylanilides also underwent cyclization to form γ-lactams (equation 110).



(109)

R^1 = H, aryl
R^2 = H, alkyl
PG = Ts, Ns
n = 1–4

27–99%

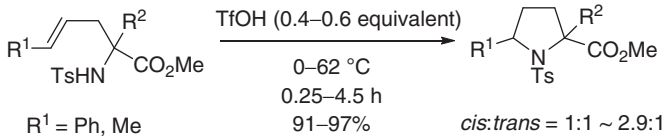


(110)

R = Ph, *p*-tolyl
R^1 = H, Me

99%

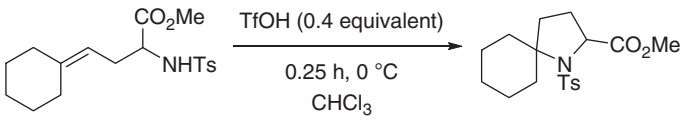
Recently, Knight et al. reported intramolecular hydroamination of homoallylic sulfonamides in the presence of triflic acid to give good to excellent yields of the corresponding pyrrolidines (equation 111).[76] Treatment of the alanine-derived sulfonamide with excess triflic acid led to a preponderance of the *cis*-isomer. *Spiro*-pyrrolidines can also be easily prepared using this acid-catalyzed intramolecular hydroamination procedure (equations 112 and 113). The method has the potentiality for elaboration of polycyclic systems by cation cyclization cascades terminated by sulfonamide function; however, it was limited to substrates not sensitive to triflic acid (equation 114). Widenhoefer et al. proved a mechanism of the intramolecular hydroamination that involves concerted, intermolecular protonation of the alkene coupled with intramolecular *anti* addition of the pendant nucleophile.[77]



(111)

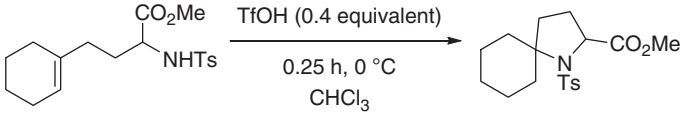
R^1 = Ph, Me
R^2 = H, Me

cis:*trans* = 1:1 ~ 2.9:1



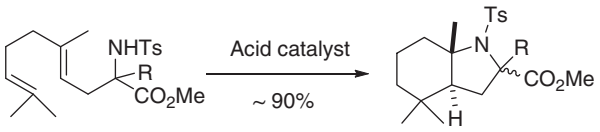
(112)

92%



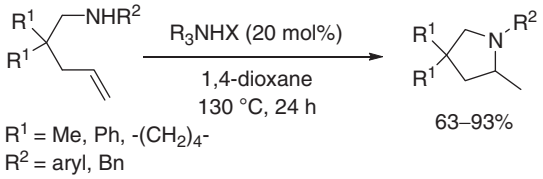
(113)

96%



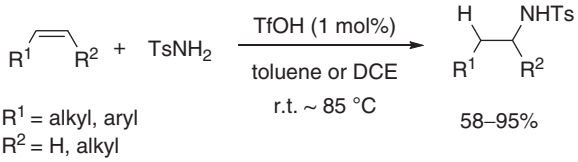
(114)

Ackermann et al. developed intramolecular hydroamination reactions of unactivated alkenes with basic alkylamines using ammonium salt of weakly coordinating anions as the catalyst.[78] The reaction conditions allowed the use of substrates bearing a variety of valuable functional groups, so bis-homoallyl amines were converted into pyrrolidines in high yields (equation 115).

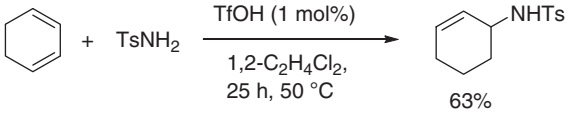


(115)

He's and Hartwig's groups independently reported that a catalytic amount (1–5 mol%) of triflic acid can efficiently promote the inter- and intramolecular additions of a broad range of N–H bond donors to unactivated olefins (equation 116).[79,80] Dienes can also undergo hydroamination under this acid conditions to form the corresponding allylamine derivatives (equation 117). The addition of benzamide to styrene also occurred at 100 °C in dioxane for more than 24 h in 77% yield (equation 118).



(116)



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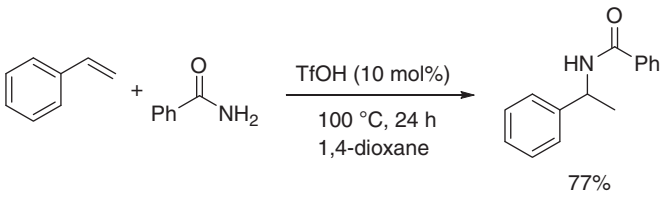
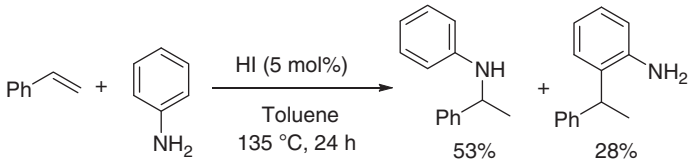


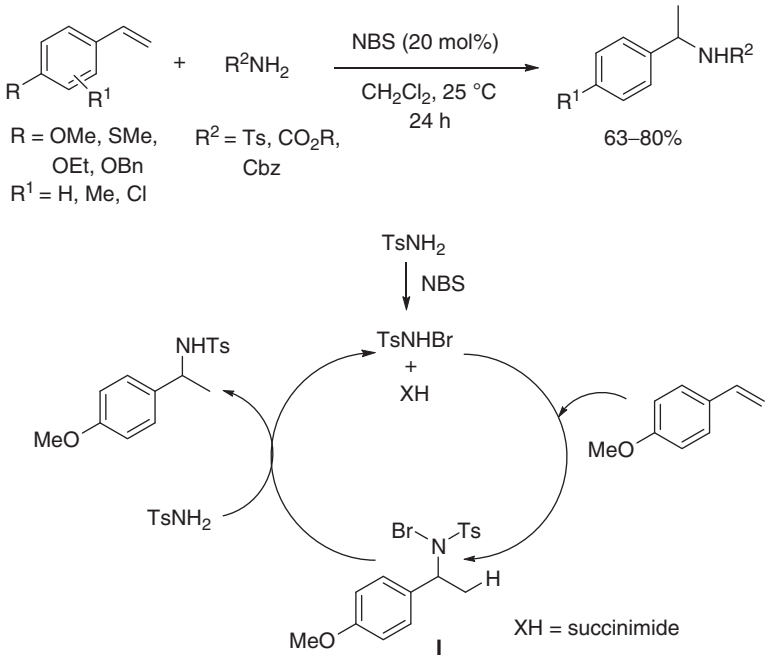
(118)

Sudalai et al. reported a NBS-catalyzed intermolecular hydroamination of activated styrenes using sulfonamides and carbamates as mild nucleophiles to produce hydroaminated products (Scheme 7).[81] The reaction was believed to proceed via intermediate TsNHBr leading to the protonation of a styrenic double bond in Markovnikov fashion. Then, regeneration of the TsNHBr species took place by the reaction of intermediate **I** with $TsNH_2$.

Hydrogen iodide has been used as a hydroamination catalyst. Marcseková and Doye found that reaction of substituted anilines with olefins in the presence of catalytic amounts of aqueous hydrogen iodide gave a mixture of the corresponding hydroamination and hydroarylation products, for example, the reaction of styrene with aniline gave 53% yield of hydroamination product along with 28% hydroarylation product (equation 119).[82] The electronic nature of the amine and the olefin plays an important role in tuning the product selectivity of the reaction. The authors suggested that a plausible mechanism for the reaction involves first an addition of hydrogen iodide to the olefin followed by a nucleophilic substitution.

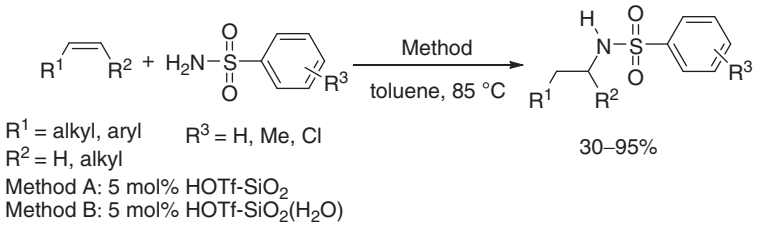


(119)



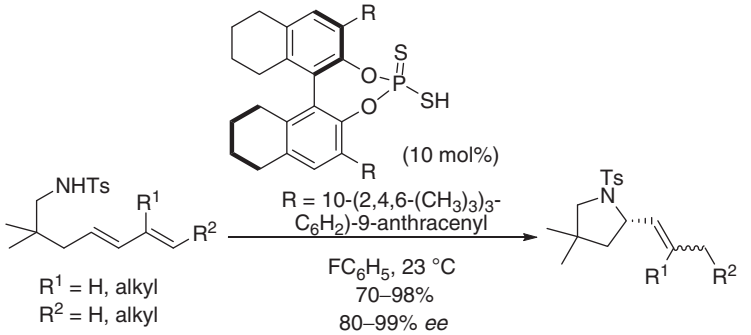
Scheme 7 NBS-catalyzed intermolecular hydroamination of activated styrenes.

Liu et al. described that two types of supported TfOH, the prepared silica gel-supported TfOH and the *in situ* silica gel-adsorbed TfOH, exhibit good catalytic activity and reusability in the hydroamination of alkene with sulfonamide. For a series of alkenes and various sulfonamides, the heterogeneous hydroamination reactions catalyzed by both types of silica gel supported TfOH to afford the products in moderate to excellent yields (equation 120).[83]

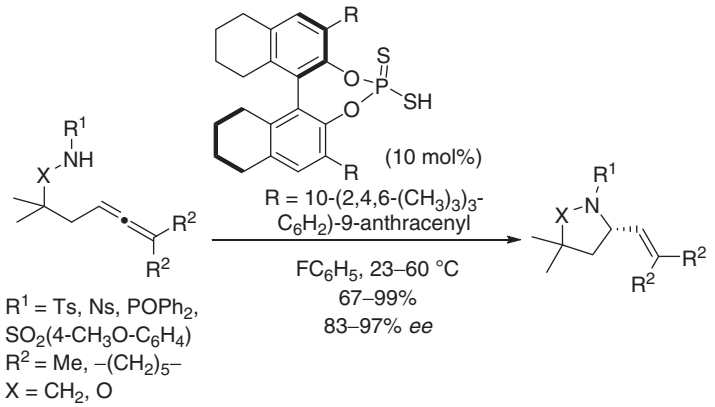


(120)

Chiral Brønsted acids were recently found by Shapiro et al. to be efficient catalysts for the intramolecular asymmetric hydroamination of dienes and allenes to generate heterocyclic products in exceptional yield with high *ee*s (equations 121 and 122).[84] The process involved the addition of acid catalyst to diene, followed by nucleophilic displacement of the resulting dithiophosphate intermediate.



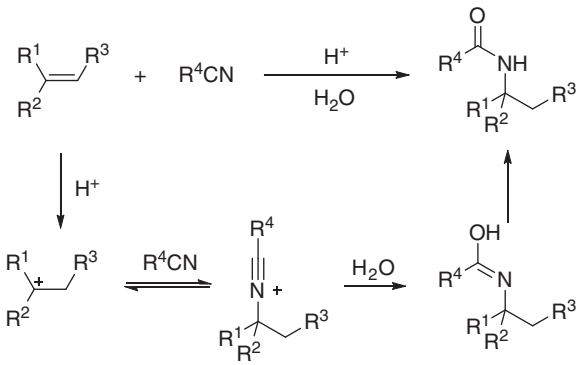
(121)



(122)

4.05.3.4 Ritter Reaction

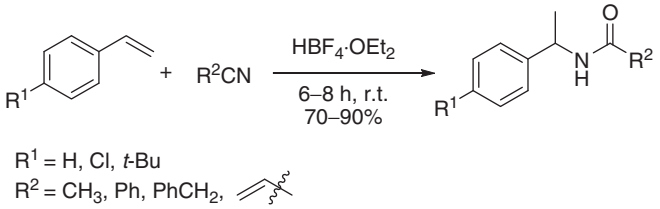
The formation of *N*-alkyl carboxamides from aliphatic- or aromatic nitriles and carbocations is known as the Ritter reaction.[85] Since its discovery, the Ritter reaction has enjoyed an enormous success and is widely used for the preparation of acyclic amides as well as heterocycles. In this reaction, a carbocation generated *in situ* from the olefin and proton is trapped by a nitrile to produce a nitrilium species, which delivers an amide after hydrolysis (Scheme 8). 1,1-Disubstituted alkenes give rise to regioisomerically pure products, but with 1,2-disubstituted alkenes a mixture of regioisomers may be formed.



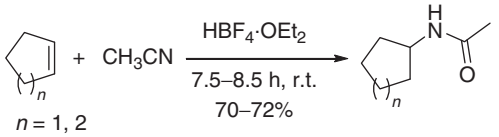
Scheme 8 Ritter reaction.

The Ritter reaction typically requires stoichiometric amounts of strong acids (usually sulfuric acid), thus limiting its application to compounds with acid-stable functional groups. In the past 20 years, remarkable progress has been made in the field of catalytic Ritter reaction in the presence of Brønsted or Lewis acids (e.g., $SnCl_4$, $BF_3{\cdot}Et_2O$, $AlCl_3$, etc.).[86]

Reddy et al. reported an efficient method for the preparation of α-aryl ethyl amides especially from vinyl arenes using an ethereal solution of tetrafluoroboric acid without any side reactions such as olefin polymerization (equation 123).[87] This method can also be applied to cyclohexene and cyclopentene to give 1-acetamidocylohexane and 1-acetamidocyclopentane, respectively, in good yields (equation 124).

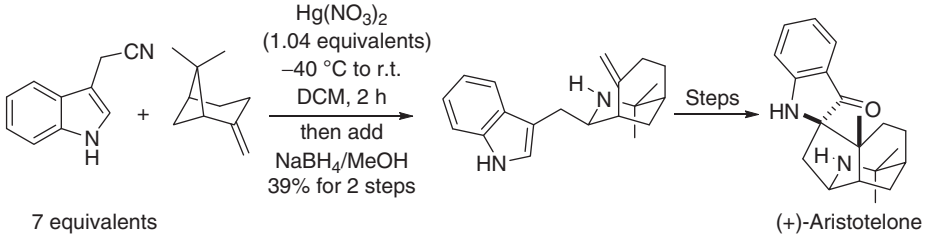


(123)



(124)

Ritter reaction has been applied in the total synthesis of natural products.[88] For example, the enantioselective biomimetic total synthesis of the alkaloid (+)-aristotelone was accomplished by Heathcock et al. [88b] The synthetic sequence commenced with a $Hg(NO_3)_2$-mediated Ritter reaction between (1*S*)-(−)-*β*-pinene and 3-indolylacetonitrile (equation 125).



7 equivalents

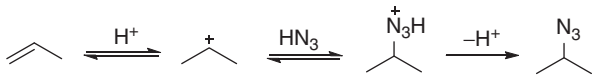
(+)-Aristotelone

(125)

4.05.3.5 Hydroazidation

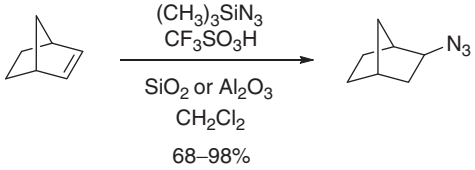
4.05.3.5.1 Addition to electron-rich alkenes

Organic azides are versatile intermediates for organic synthesis. The hydroazidation of C–C multiple bonds is one of the efficient methods for synthesis of organic azides. In an earlier report, a direct and regiospecific route to alkyl azides by acid or Lewis acid-catalyzed addition of HN_3 to certain alkenes was explored.[89] The acid-catalyzed reactions proceed through a carbocation intermediate formed by protonation of the double bond, followed by nucleophilic attack of HN_3 and subsequent loss of a proton (equation 126).



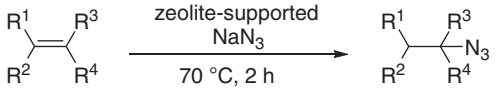
(126)

Kropp et al. reported a surface-mediated addition reaction of hydrazoic acid to alkenes.[90] Silica gel and alumina facilitate the protonation of alkenes and this reaction can be applied to the synthesis of tertiary, benzylic, and allylic azides (equation 127).



(127)

Sreekumar established a facile heterogeneous catalytic method for the conversion of electron-rich alkenes into the corresponding azides, using zeolite-supported sodium azide reagents (equation 128).[91]

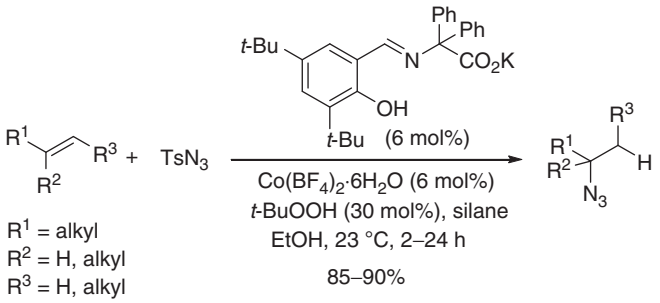


R^1 = H, Me, Ph
R^2 = Me, Et, Ph
R^3 = H, Me
R^4 = H, Me

69–94%

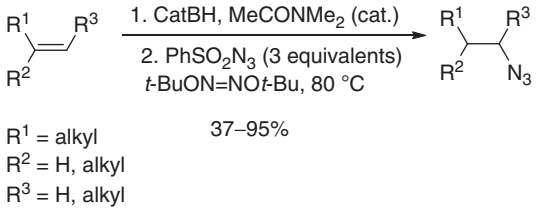
(128)

The direct reaction of alkenes with hydrazoic acid sources is limited to alkenes that give rise to stabilized carbocations and require excess HN_3, $TMSN_3$, or zeolite-supported NaN_3. Unactivated monosubstituted olefins have been described as unactivated in these processes. Recently, Carreira et al. developed a new method to address this unreactive issue by applying a simple cobalt catalyst prepared *in situ* from Schiff base and $Co(BF_4)_2{\cdot}6H_2O$, leading to alkylazides from unreactive alkenes and sulfonyl azides, with high Markovnikov selectivity (equation 129).[92] The reaction is believed to proceed via a radical process and thus *tert*-butyl hydroperoxide is crucial to this transformation.

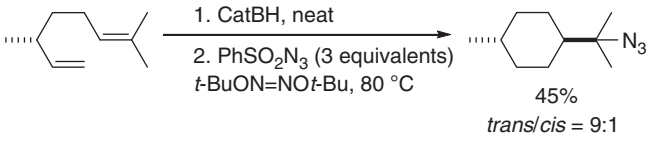


(129)

An anti-Markovnikov hydroazidation of alkenes is realized by a two-step process involving hydroboration with catecholborane (CatBH) followed by the reaction with benzenesulfonyl azide in the presence of a radical initiator.[93] This procedure is applicable to a wide range of alkenes and gives excellent results with mono-, di-, and trisubstituted alkenes (equation 130). *β*-Citronellene underwent 6-*exo*-trig cyclization to afford the corresponding organic azide at a high concentration of benzenesulfonyl azide (equation 131).



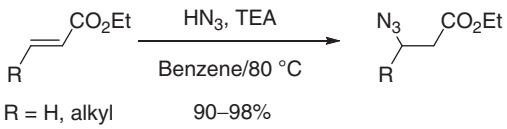
(130)



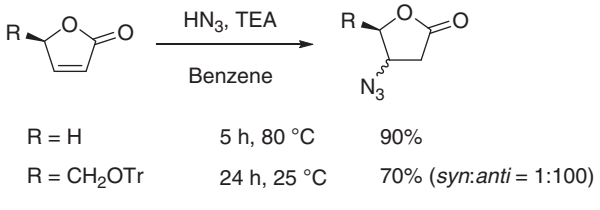
(131)

4.05.3.5.2 Addition to electron-deficient alkenes

An efficient base-catalyzed conjugate addition of hydrogen azide to enoates to form *β*-azido esters or lactones was reported by Rao et al. (equations 132 and 133).[94] The latter one is highly disatereoselective.

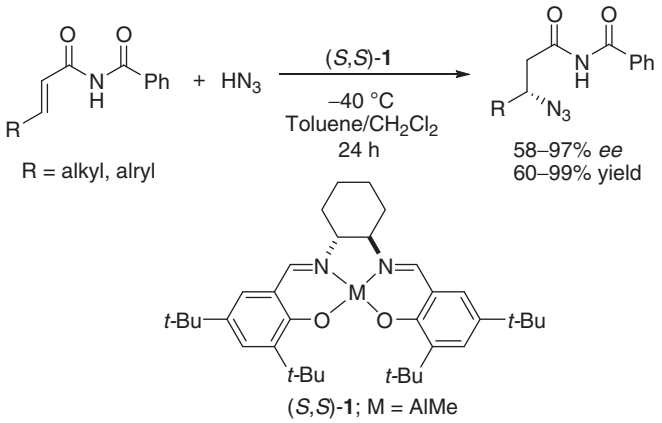


(132)



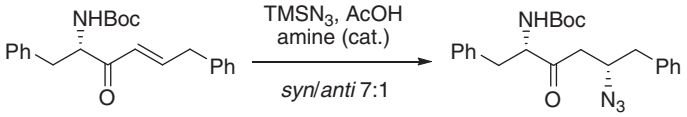
(133)

A highly enantioselective conjugate addition of hydrazoic acid to *α,β*-unsaturated imides catalyzed by a readily available chiral (salen)Al(III) complex was observed (equation 134).[95] The aluminum catalyst is fulfilling only one of those functions, that is, either as Lewis acid or as mediator of azide transfer in the conjugate addition to unsaturated imides.



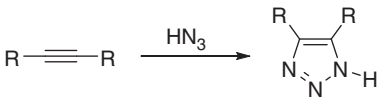
(134)

Considering that hydrazoic acid is a highly toxic and explosive reagent, efforts have been denoted to find other precursors instead of hydrazoic acid. Benedetti et al. reported $TMSN_3$/AcOH system for hydroazidation of amino acid-derived α,β-unsaturated ketone to give β-azido carbonyl compound (equation 135).[96] The stereoselectivity was controlled by the remote stereocenter present on the substrate.



(135)

The reaction of hydrazoic acid with alkynes generally provides triazoles via a click process instead of azides rather than the hydroazidation (equation 136).[97]



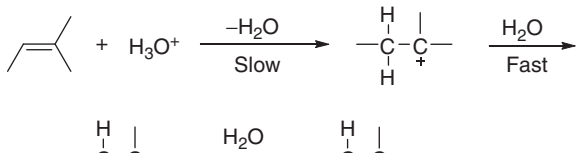
(136)

4.05.4 H–O Addition

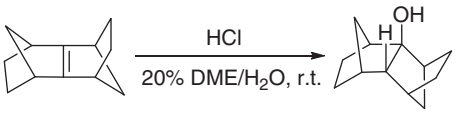
4.05.4.1 H–OH Addition

The addition of H–OH to C–C multiple bonds, which is often called hydration reaction, is a fundamental organic transformation that has been long studied.[98] The catalyst was mercury(II) salt, which allows hydration of alkenes and alkynes in good yields.[99] Recent efforts have been expended to find new catalysts including transition metals catalysts such as Ru, Rh, Pd, Pt, and Au.[100]

The acid-catalyzed addition of H_2O to alkenes is a highly synthetic useful reaction, which converts an alkene into an alcohol in a Markovnikov fashion (equation 137).[101] The mechanistic studies show that the protonation of alkenes to give a carbocation intermediate is a rate-determining step. This step is irreversible under hydration conditions and the reaction is of first order in both alkene and hydronium ion. Thus, electron-donating groups on C=C bond would accelerate this electrophilic addition step, whereas electron-withdrawing groups would decelerate it. This hydration is also applicable to steric alkenes (equation 138).[102]

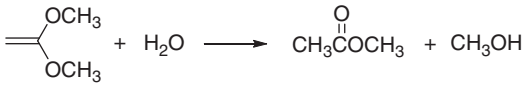


(137)



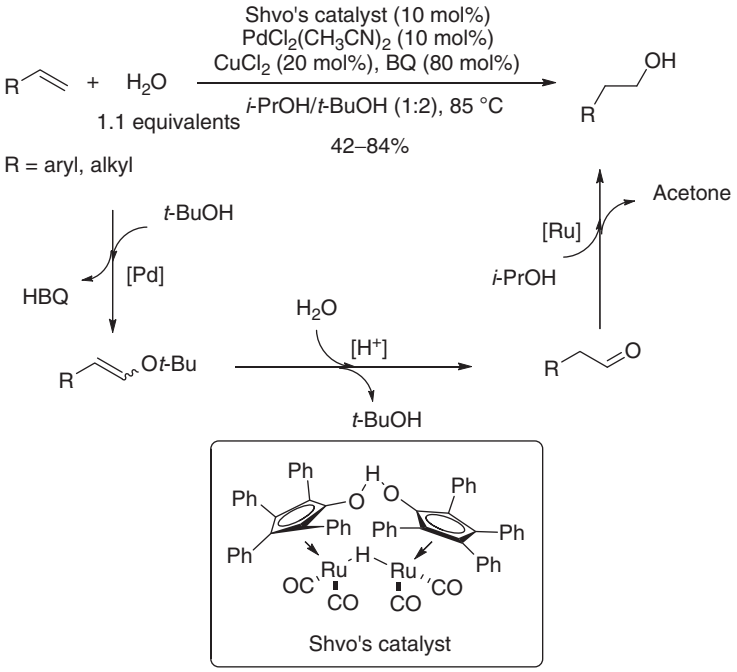
(138)

The acid-catalyzed hydrolysis of 1,1-dimethoxyethene gave methyl acetate, which is believed to proceed via a dialkoxy cation followed by decomposition of the hydrogen ortho ester hydration product (equation 139).[103]



(139)

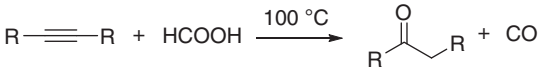
An anti-Markovnikov's selective hydration of alkenes and alkynes has been recently observed by applying metal-catalyst. For example, Grubbs reported the addition of water across olefins to form primary alcohols by using a triple relay catalysis system that couples palladium-catalyzed oxidation, acid-catalyzed hydrolysis, and ruthenium-catalyzed reduction cycles (Scheme 9).[104] He postulated that in the presence of *t*-BuOH, the olefin would first undergo Pd-catalyzed oxidation to generate a *t*-butyl vinyl ether. Owing to the bulkiness of *t*-BuOH, the linear vinyl ether is preferred. Subsequently, in the presence of water, ether would be converted to aldehyde through acid-catalyzed hydrolysis. Finally, aldehyde would be reduced to primary alcohol via Ru-catalyzed transfer hydrogenation reaction.



Scheme 9 Pd/Ru-catalyzed hydration of functionalized styrenes and 1-octene.

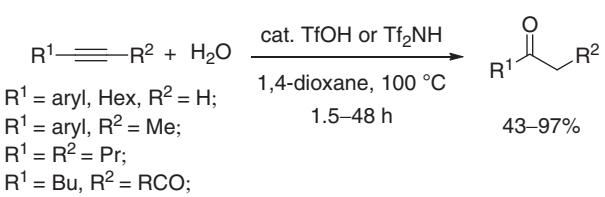
4.05.4.1.1 Addition to alkynes

Many alkynes are hydrated in refluxing formic acid; notably, formic acid catalyzes its own addition to the alkyne, and the intermediary enol formate undergoes hydrolysis readily under the reaction conditions (equation 140).[105] In this case, formic acid serves as a formal water donor.

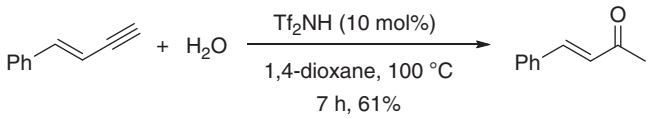


(140)

The hydration of alkynes using a catalytic amount of Brønsted acid, trifluoromethanesulfonic acid, or trifluoromethanesulfonimide provided a practical and convenient process to give a wide variety of carbonyl compounds with perfect regioselectivity for alkynes with different electronic nature substituents (equation 141).[106] 1,3-Conjugated enynes allowed the selective addition of water exclusively to the C–C triple bond to give the corresponding methyl enones (equation 142). The mechanism of the reaction involves formation of an alkenyl cation intermediate, followed by nucleophilic attack of water and tautomerization to ketones.

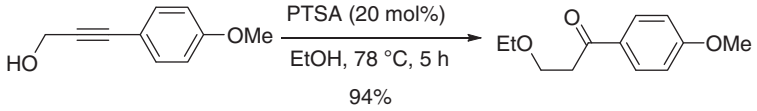


(141)



(142)

A mild protocol for hydration of aryl-substituted alkyne under the catalysis of PTSA in EtOH for the synthesis of alkyl aryl ketones has been developed by Alami et al.[107] This mild protocol allows the hydration reaction to occur in the presence of free hydroxyl group and nonactivated carbon–carbon triple bond (equation 143).

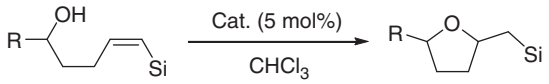


(143)

4.05.4.2 H–OR Addition

Direct additions of ROH to nonactivated C–C multiple bonds, so-called hydroalkoxylation reaction, offer in principle a straight, atom-economical process for synthesis of ethers. Recently, transition metal-catalyzed intramolecular hydroalkoxylations of alkenes, alkynes, and allenes have emerged largely to afford O-containing heterocycles, which will be discussed in related chapter in this volume. In this part, only acid-catalyzed hydroalkoxylation of alkenes and alkynes are introduced (*see* Chapter 4.07).

In the presence of a catalytic amount of TsOH or $TiCl_4$, silylated alkenes bearing a tethered hydroxyl group are easily cyclized to THFs and tetrahydropyrans by stereospecific *exo-trig syn*-addition (equation 144).[108] A plausible mechanism for this cyclization involves the formation of a β-silylcarbenium ion intermediate by protonation of the sp^2 carbon α to the silyl group and subsequent intramolecular attack of the hydroxyl oxygen to the carbenium ion center. The cyclized products can be converted into the corresponding alcohols by oxidative cleavage of the Si–C bond. Interestingly, 1,2-silyl migrative cyclization of α-substituent vinylsilanes bearing a hydroxyl group is valuable in the stereoselctive synthesis of certain cyclic ethers (equation 145).[109] The presence of an alkyl group as R is essential to the 1,2-silyl migration, which is reasonable because the alkyl group stabilizes the rearranged carbenium ion. Indeed, the isomerizations of (2*R*,1*S*)-**1** and (2*R*,1*R*)-**1** to tetrahydropyran **2** rapidly proceeded with inverse stereoselectivity (equation 146).

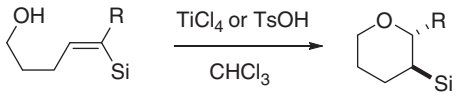


Si = $SiMeR^1R^2$
R = aryl, alkyl

TsOH, 60 °C, 1.3–16 h — 66–95%, *trans*:*cis* = 60:40 ~ 91:9

$TiCl_4$, 25 °C, 0.3–25 h — 68–98%, *trans*:*cis* = 66:34 ~ 93:7

(144)

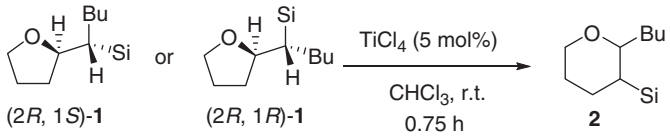


Si = $SiMeR^1R^2$
R = alkyl

72–93%

trans:*cis* = 97:3 ~ >99:1

(145)



(2*R*, 1*S*)-**1** or (2*R*, 1*R*)-**1**

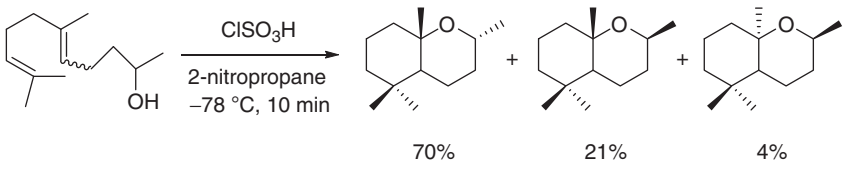
Si = $SiMe_2$-*t*-Bu

2

91% (*trans*/*cis* = 95/5) from (2*R*, 1*S*)-**1**
85% (*trans*/*cis* = 2/98) from (2*R*, 1*R*)-**1**

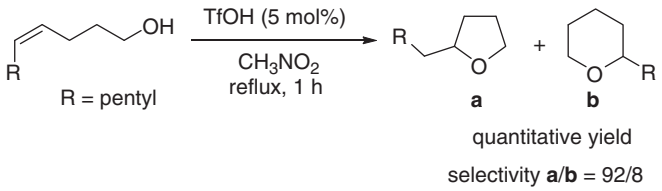
(146)

The stoichiometric amount of superacid $ClSO_3H$ can also be used for electrophilic olefin cyclizations with internal nucleophilic termination in a chemically selective and stereospecific way (equation 147).[110]

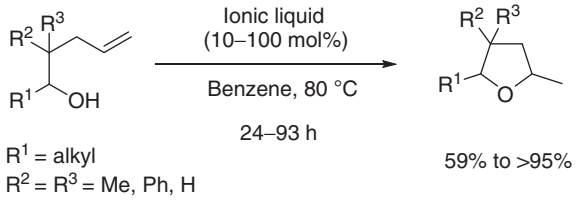


(147)

Duñach et al. reported a cyclization of unsaturated alcohols to the corresponding cyclic ethers in quantitative yield, using 0.1–5 mol% of triflic acid in dichloromethane or nitromethane (equation 148).[111] Substituted THFs or tetrahydropyrans were regioselectively obtained depending on the substitution of alkenes. The cyclizations can also occur in the SO_3H-tethered imidazolium or triazolium Brønsted acidic ionic liquids in a Markovnikov manner (equation 149).[112] For 6-methyl-5-hepten-2-ol, these two systems are both effective to afford the corresponding tetrahydropyran in excellent yields (equation 150). The latter protocol has been successfully applied to the synthesis of (±)-centrolobine.



(148)



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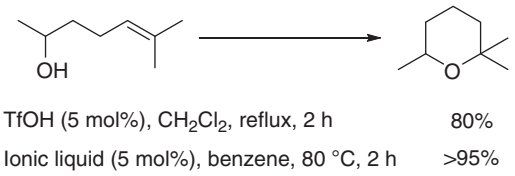
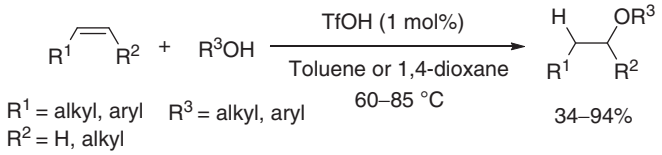


(150)

Hartwig et al. have shown that triflic acid in weakly basic solvents catalyzes the hydroalkoxylation of unactivated alkenes (equation 151).[79] Cyclization of olefins in the presence of triflic acid takes place at the more substituted carbon of olefin because the corresponding carbocation intermediate is more stable (equation 152).



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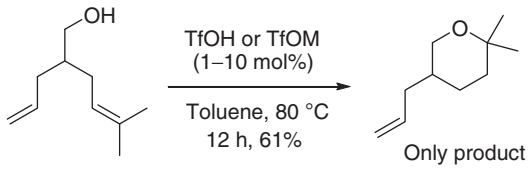
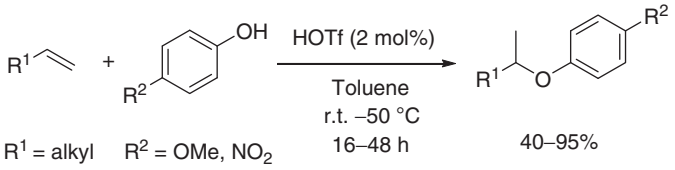


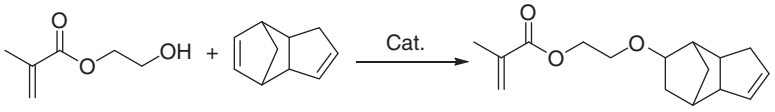
(152)

At the same time, He et al. described this triflic acid procedure for intermolecular addition of phenols to inert olefins under mild conditions, leading to phenol ethers in 40–95% yields (equation 153).[80]



(153)

During the study of $Cu(OTf)_2$-catalyzed hydroalkoxylation of dicyclopentadiene and norbornene with 2-hydroxyethyl methacrylate, Carpentier et al. through kinetics, electron spin resonance, and catalyst-poisoning experiments found that triflic acid is the true active catalyst in these reactions (equation 154).[113] These products are industrially important relevant monomers. Reduction of $Cu(OTf)_2$ by the olefin reagent is the main (if not exclusive) pathway for generation of triflic acid.



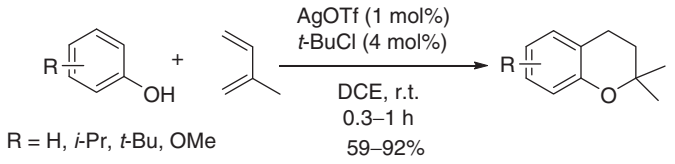
(154)

$Cu(OTf)_2$ (1 mol%), 80 °C, 2 h, 90%

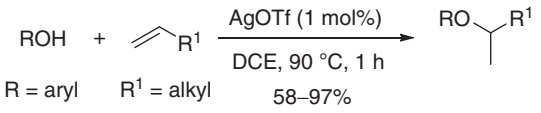
$Cu(OTf)_2$ (1 mol%), 100 °C, 0.5 h, 90%

TfOH/BHT (0.1/0.01 mol%), 100 °C, 4 h, 90%

Similarly, Hintermann et al. found that a hidden Brønsted acid from AgOTf and a chlorinated solvent was true catalytic species in hydroalkoxylation reactions. Either the 'hot' (AgOTf+DCE at reflux) or the 'cold' (AgOTf+*t*-BuCl) protocol gave highly active catalysts for the addition of phenols to isoprene, which involves a Friedel–Crafts alkylation followed by a hydroalkoxylation (equation 155).[114] Catalytic intramolecular hydroalkoxylations of allylphenols could be achieved by the 'hot' protocol (equation 156).

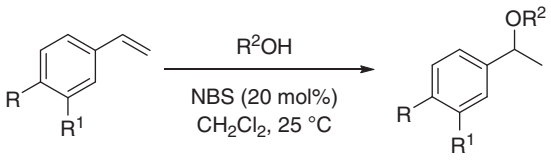


(155)



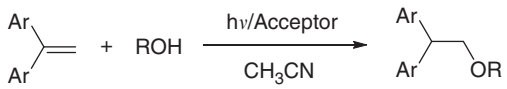
(156)

Similar to hydroamination reaction, the hydroalkoxylation of activated styrenes can also be promoted by NBS under ambient conditions by using alcohols as mild nucleophiles to produce the corresponding ethers in good yields (equation 157).[81]



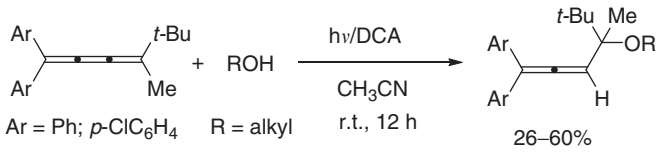
(157)

Mizuno et al. reported that photoaddition of alcohols to arylalkenes such as 1,2-diarylethene or styrene derivatives in the presence of an electron-accepting photosensitizer gave the corresponding product resulting from anti-Markovnikov addition regioselectively (equation 158).[115]



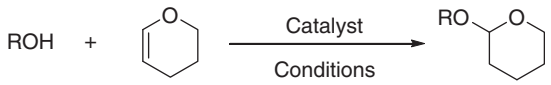
(158)

This photoinduced addition could be extended to 1,1-diaryl-1,2,3-butatriene derivatives to selectively give allene products (equation 159).[116]



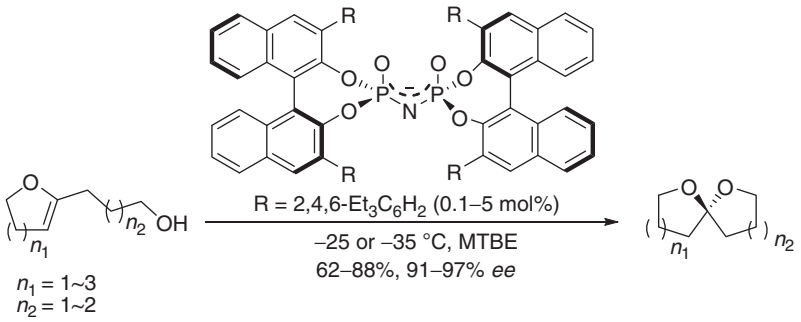
(159)

The acid-catalyzed reaction of alcohols and phenols with 3,4-dihydro-2H-pyran to give tetrahydropyranyl-substituted ether is a classic and one of the most common strategies for the protection of hydroxyl functions (tetrahydropyranylation, equation 160).[117] Various Brønsted acids[118] and a large variety of Lewis acids[119] have been utilized to catalyze this reaction. Besides, tetrahydropyranylation have been carried out using iodine microwave irradiation,[120] ionic liquids,[121] benzyltriphenylphosphonium tribromide,[122] pyridinium chloride,[123] thiourea,[124] etc.



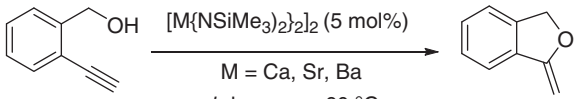
(160)

Recently, List et al. designed and synthesized the confined Brønsted acids on the basis of a C_2-symmetric imidodiphosphoric acid motif, enabling a catalytic highly enantioselective spiroacetalization reaction (equation 161).[125]

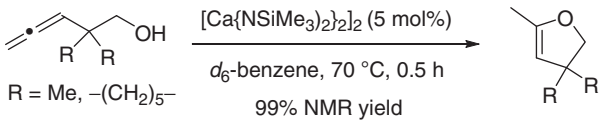


(161)

The addition of alcohols to alkynes is a facile access to enol ethers and oxygen-containing heterocycles.[126] More recently, many transition metals proved to be efficient catalysts for intramolecular cyclizations of alkynyl alcohols.[127] Barrett et al. have demonstrated heavier alkaline earth bis(TMS) amide derivatives as effective precatalysts to mediate intramolecular hydroalkoxylation/cyclization of alkynyl alcohols (equation 162).[128] Although the basicity of the $[M(N(SiMe_3)_2)_2]_2$ precatalysts opens up isomerization pathways for less-activated alkynyl alcohols, all three metal complexes show good catalytic activity for terminal and internal alkynyl primary alcohols. Allenyl alcohol substrates were found to cyclize and provide the endocyclic enol ether as the sole isomeric product (equation 163).

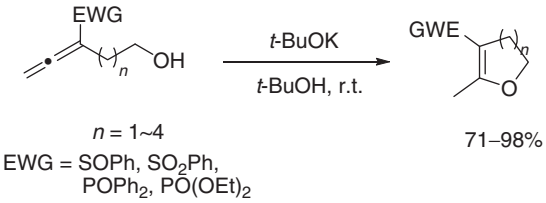


(162)



(163)

Many strategies have been developed for the base-promoted ring-closing reaction of allenyl alcohols.[129] For example, Mukai et al. reported a reliable and efficient procedure for constructing five- to eight-membered oxacycles in high yields (equation 164).[130] In these procedures, the allenyl compounds possessing an electron-withdrawing group undergo endo-mode cyclization at the sp-hybridized carbon center. Although the utility of transition metal catalysts[131] for the hydroalkoxylation of allenes has received much attention, it does not fall within the scope of this chapter.

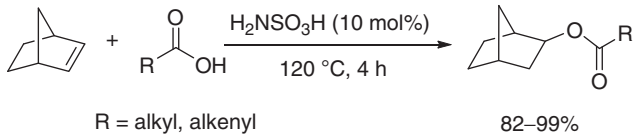


(164)

4.05.4.3 H–O_2CR Addition

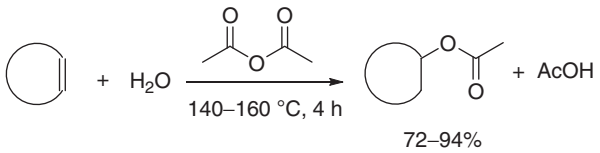
The addition of carboxylic acids to alkenes, that is, the hydrocarboxylation or hydroesterification provides carboxylic esters. In general, the additions take place in the Markovnikov fashion under the catalysis of Brønsted or Lewis acids.

Yang et al. observed the addition reaction of aliphatic acids to cyclic olefins in the present of catalytic amount of sulfamic acid (equation 165).[132] The catalyst could be recycled easily by filtration and directly reused in the next run with satisfactory results. Unfortunately, this method is not applicable to acyclic olefins.



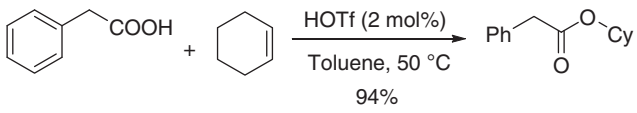
(165)

Mamedov et al. used carboxylic acid anhydrides and water to achieve the hydrocarboxylation of cage-like cyclic olefins (equation 166).[133] High reaction temperature is necessary to make the reaction occur.

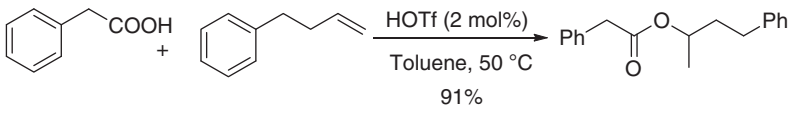


(166)

He et al. recently demonstrated that catalytic amount of TfOH is efficient to promote the hydroesterification of a general scope of olefins. The reaction proceeds smoothly at 50 °C with 2% HOTf as the Brønsted acid catalyst (equations 167 and 168).[80] The regioselectivity depends on the stability of the carbocation intermediate.



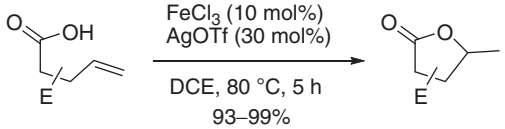
(167)



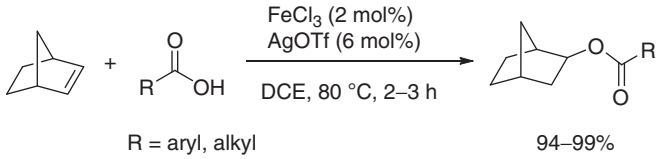
(168)

The reaction of 1-octene with carboxylic acids leading to esters with better fuel properties in the presence of sulfonic acid resin was demonstrated as partial bio-oil upgrading models.[134]

Efficient additions of carboxylic acids to alkenes can be catalyzed by transition metals such as Au, Ag, Ru, Pt, and Cu under relatively mild conditions.[135] Besides these transition metals, cationic iron salts were found to be good catalysts for intra- and intermolecular addition of carboxylic acids to olefins, which afforded the corresponding esters in good yields (equations 169 and 170).[136]

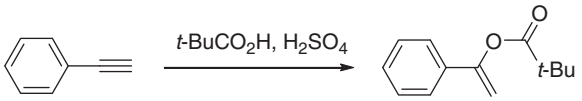


(169)



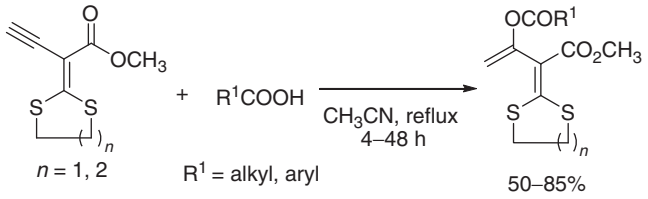
(170)

The addition of carboxylic acids to alkynes affords enol esters, which are useful intermediates in organic synthesis. Simple sulfuric acid catalyst has been employed to catalyze this addition (equation 171).[137] Originally, the catalytic addition of carboxylic acids to alkynes was carried out in the presence of Zn and Hg salt or strong acids.[138] Later on, the reactions relying on the transition metal complexes, such as palladium, rhodium, iridium, ruthenium, and rhenium, were developed.[139]



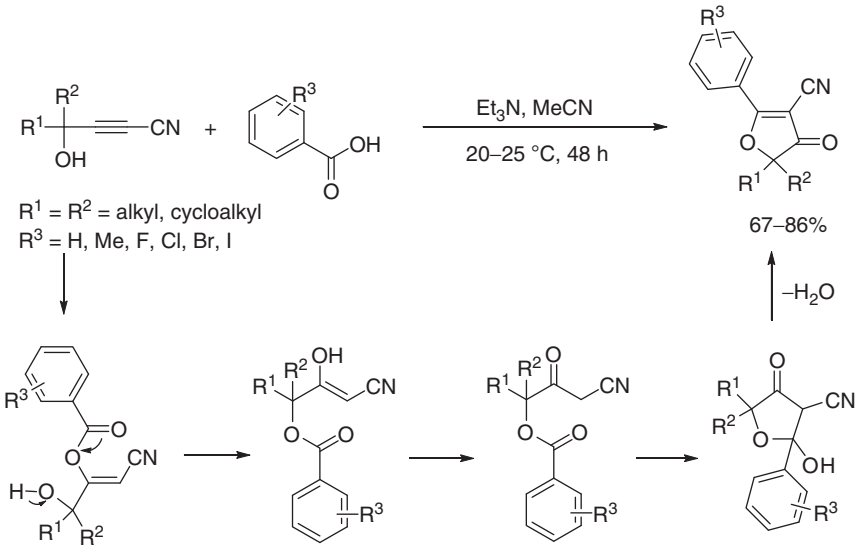
(171)

A few examples have apparently been carried out on the addition of carboxylic acids to alkynes without metal. Recently, Zhao and Liu reported the chemo- and regioselective addition of carboxylic acids to the alkylthio-activated terminal alkynes in moderate to good yields in the absence of catalysts (equation 172).[140] The authors proposed that the terminal carbon atom of the carbon–carbon triple bond was more electron rich, which afforded products in the Markovnikov fashion.



(172)

Trofimov et al. discovered a domino reaction of available α,β-acetylenic γ-hydroxy nitriles and arenecarboxylic acids to give 4-cyano-3(2*H*)-furanones in 67–86% yield (**Scheme 10**).[141] The reaction is triggered by the addition of an arenecarboxylic acid to a triple bond, followed by the domino reaction sequence: intramolecular transesterification-enol formation and Claisen condensation of the ketoacetonitrile tautomer with ester functional group.



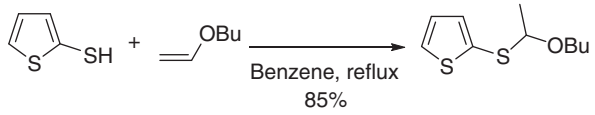
Scheme 10 Domino sequence leading to 3(2*H*)-furanones.

4.05.5 H–SR Addition

The addition of thiols onto carbon–carbon double bonds may proceed via an electrophilic pathway involving ionic processes or a free-radical chain pathway.[142] Usually, the free radical course promotes anti-Markovnikov addition, whereas the ionic process

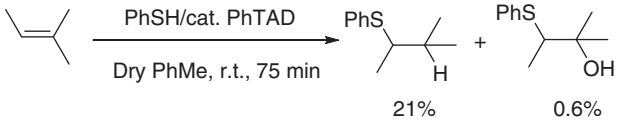
leads to Markovnikov adducts. The main emphasis in the literature has been on the free-radical pathway and little work exists on the electrophilic pathway. Some overlaps may not be avoided with the chapter dealing with the radical addition (*see* Chapter 4.12).

In earlier report, heteroaromatic thiol reacted with an electron-rich olefin (butyl vinyl ether) under nonradical conditions to give the electrophilic adduct in good yield through an ionic stepwise mechanism (equation 173).[143]



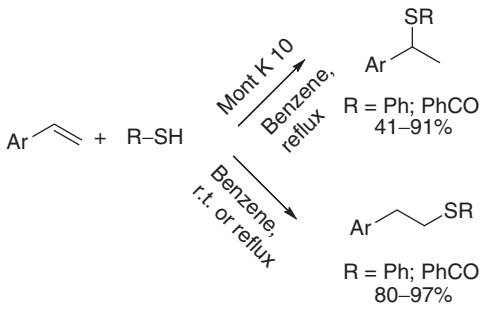
(173)

N-Phenyltriazolinedione(PhTAD) was found to be an efficient initiator in the radical (anti-Markovnikov) addition of thiophenol to 2-methyl-2-butene (equation 174).[144] A trace amount of hydroxy-sulfide was also isolated, which is formed possibly from the oxyen trapped in the radical intermediate.



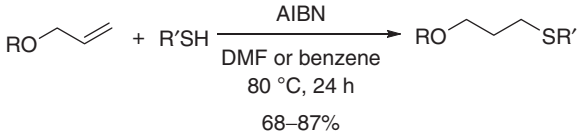
(174)

Benicewicz described the regioselective addition of thiophenol and thiobenzoic acids onto various olefins (equation 175).[145] In the absence of any catalyst, the S–H addition took place in an anti-Markovnikov fashion, leading to the linear adduct in high yields. The formation of anti-Markovnikov products may be explained by presuming that the addition of S–H onto C═C bonds took place in a concerted manner with steric factors controlling the regioselectivity. However, in the presence of Lewis acids, such as clays (e.g., $AlCl_3$, etc.), the S–H addition onto C═C bonds proceeded in a Markovnikov manner, giving branched adducts in high yields. This process generated the more stable benzylic carbocations followed by subsequent attack of the sulfur nucleophiles.



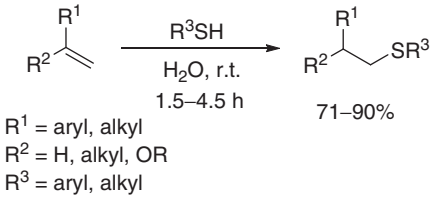
(175)

Polymer-supported cyclitol allyl ethers were ready for the free radical addition with alkyl, substituted alkyl, and benzyl thiols (equation 176).[146] This free radical reaction occurs with anti-Markovnikov regiospecificity on terminal alkenes. Cleavage of the reaction products from the polymer support affords good to excellent yields of thioethers.



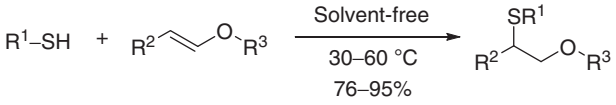
(176)

Later, Ranu and Mandal developed a simple protocol for the anti-Markovnikov addition of thiols to alkenes in water without any additive (equation 177).[147] It was assumed that water promoted the reaction through hydrogen bond formation with the sulfhydryl hydrogen of the thiol and thus increased the nucleophilicity of the thiolate ion.



(177)

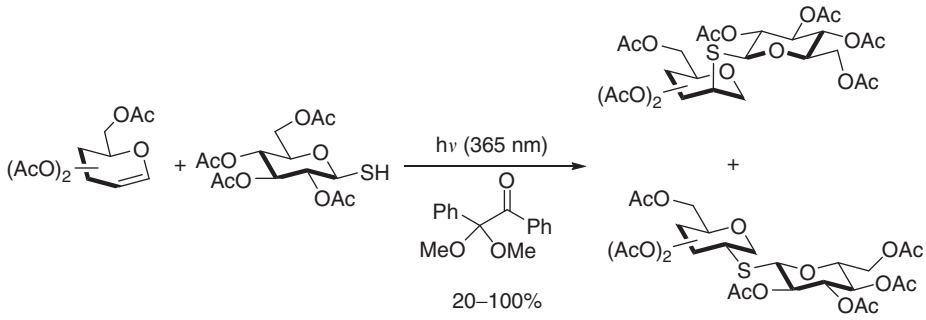
A convenient synthesis of the anti-Markovnikov product by addition of thiols to vinyl ethers in solvent-free conditions without the use of a catalyst was reported by Lin (equation 178).[148] The interaction between oxygen in vinyl ether and hydrogen in thiol could activate the C–C double bond.



(178)

R^1 = Ph, Bn, CH_3CO, $CH_3(CH_2)_2CH_2$, $CH_3(CH_2)_{10}CH_2$;
R^2,R^3 = CH_2-CH_2CH_2, CH_2-CH_2; R^2 = H; R^3 = C_2H_5, *n*-C_4H_9

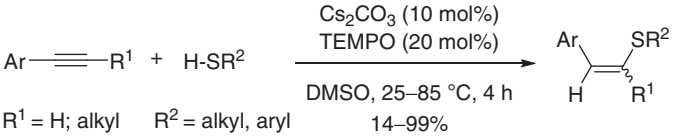
It has recently been demonstrated that glycals can undergo a photoinduced addition of glycosylthiyl radicals with total regioselectivity to give 1-deoxy *S*-disaccharides in good to excellent yields (equation 179).[149]



(179)

The 1,4-addition of thiols to electron-deficient olefins to form a carbon–sulfur bond constitutes a key reaction in biosynthesis as well as in synthetic organic chemistry. Usually, this conjugate addition is based either on the activation of thiols by base or on the activation of the acceptor olefins with Lewis acids.[150] This part will be discussed elsewhere in this series.

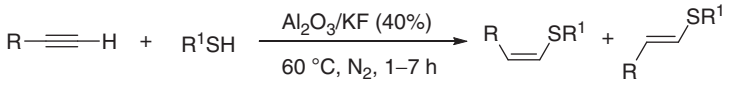
Base-mediated addition of thiols to alkynes (hydrothiolations) is a well-known process and proceeds mostly in an anti-Markovikov manner. Yorimitsu and Oshima reported a base-catalyzed addition reaction between alkynes and thiols.[151] The reaction proceeded in the presence of 10 mol% Cs_2CO_3 and 20 mol% radical inhibitor (TEMPO) to provide 1-alkenyl alkyl sulfides (equation 180).



(180)

R^1 = H; alkyl R^2 = alkyl, aryl

Several vinyl sulfides could be prepared directly under solvent-free conditions using solid-supported catalyst (Al_2O_3/KF). The method selectively furnished the corresponding anti-Makovnikov vinyl sulfides in good to excellent yields (equation 181).[152]

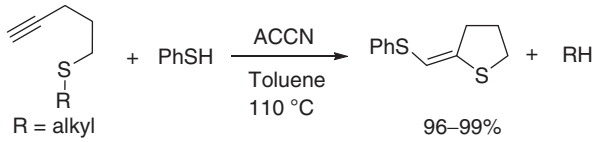


(181)

R = CH_2OH, $C(CH_3)C_2H_5OH$, CH_2CH_2OH, $C(CH_3)_2OH$, C_6H_5, C_5H_{11}
R^1 = C_6H_5, *p*-ClC_6H_4, $C_{12}H_{25}$

Z:*E* = 2:98 ~ 86:14

Benzenethiol can also be used in the radical cyclization reaction. For example, the radical reaction of alkyl 4-pentynyl sulfides and benzenethiol generated thiophene derivatives (equation 182).[153] The mechanism involves addition of benzensulfanyl radical to the triple bond of sulfide to give vinyl radical, which gives rise to homolytic substitution at the sulfur atom to afford the desired alkyl radical together with the products.

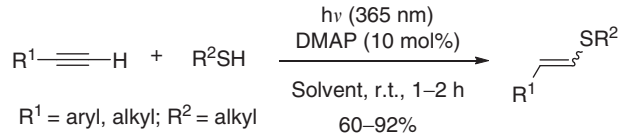


(182)

R = alkyl

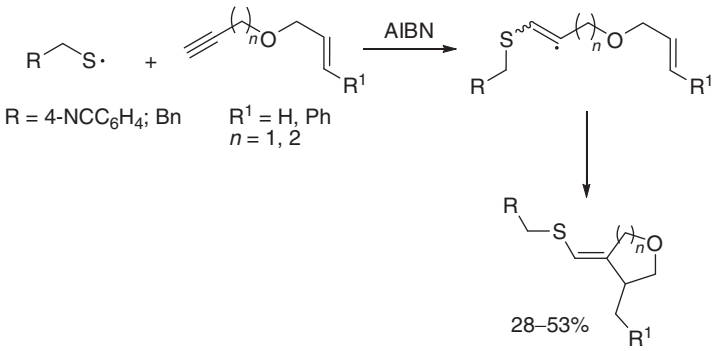
96–99%

The free-radical thiol-ene addition reactions between aliphatic or aromatic alkynes and alkanethiols were reported by Nanni et al. (equation 183).[154] A proper choice of the reaction conditions can hence favor highly selective occurrence of either mono- or bis-sulfide addition product. In comparison with alkylacetylenes, the aromatic alkynes work better to form the monocoupling products exclusive of the double-addition ones.



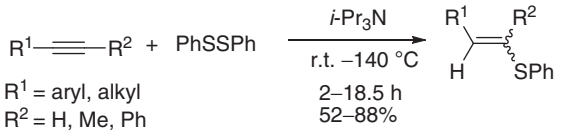
(183)

Sulfanyl radical addition to the employed enynes was generally found to be regioselective to the C–C triple bond, which can undergo five- or six-membered cyclization onto styrene or the alkene double bond (equation 184).[155]

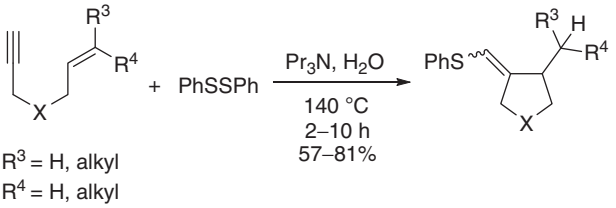


(184)

Ishibashi et al. developed a method for the formation of benzenethiyl radical from diphenyl disulfide with tripropylamine via a single-electron transfer reaction.[156] Treatment of a mixture of diphenyl disulfide and alkynes with tripropylamine gave vinyl sulfides in moderate to good yields (equation 185). The method can also be applied to radical cyclizations of eneyne compounds (equation 186).

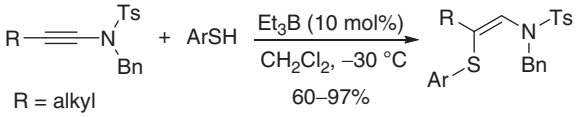


(185)



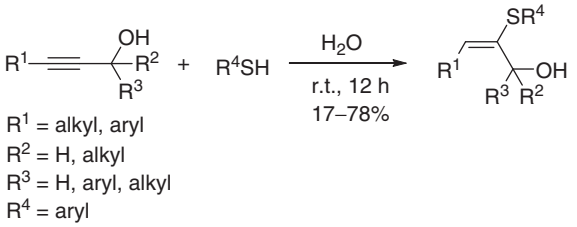
(186)

Mixing ynamides and arenethiols in the presence of a catalytic amount of triethylborane affords the corresponding adducts, (*Z*)-1-amino-2-thio-1-alkenens, in 60–97% yields with high selectivity (equation 187).[157]

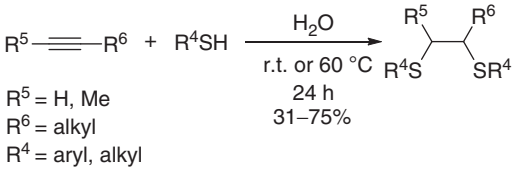


(187)

Nonterminal propargyl alcohols react with aryl thiols in water to produce a highly regio- and stereoselective hydrothiolation product, (*E*)-alkenyl thioether (equation 188).[158] The thiol only attacked the carbon next to the alcohol. The reason for the high regioselectivity can be explained by the relative stability of vinyl radical intermediates, and the one for the high stereoselectivity can be explained by the steric factors. Furthermore, this method can also be used for dihydrothiolation of alkynes by using water as the sole solvent to prepare vicinal dithioethers (equation 189).

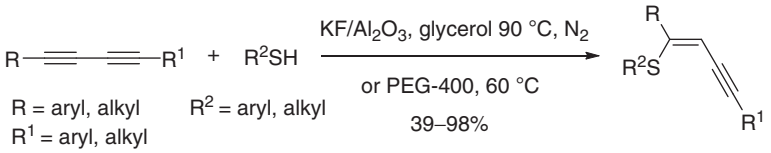


(188)



(189)

The addition of thiol to 1,3-butadiynes has been recently reported by Perin et al. The reaction is promoted by KF/Al_2O_3 and can be performed using glycerol or polyethylene glycol (PEG) as solvents to give the corresponding alkenyl sulfides preferentially with *Z*-configuration (equation 190).[159]



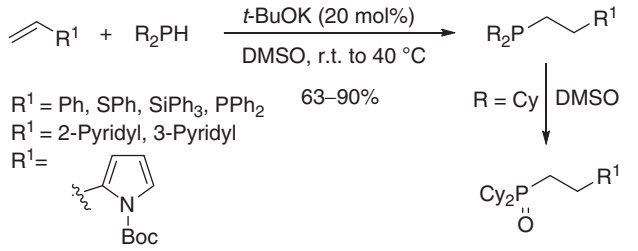
(190)

4.05.6 H–P Addition

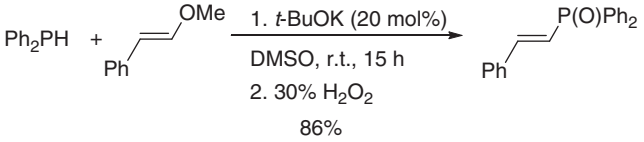
The addition of phosphines to alkenes and alkynes has been studied, which requires radical initiation, transition metal catalysis, or strong basic conditions. The use of phosphine–borane complexes is also possible and allows selective hydrophosphination. In recent years, the phospha-Michael reaction of activated alkenes has been promoted, which is not discussed in this chapter (*see* Chapter 4.01).

Koenig et al. concluded that when phosphorus atom bears an oxygen or sulfur atom, the mechanism might be either radical or ionic, depending on the nature of the substrate, irrespective of the experimental method used. For the substrate having a nucleophilic character, the mechanism is preferentially radical, and for the one containing an electron-withdrawing substituent, the main mechanism is ionic. When the phosphorus atom is not oxidized, there is a duality of the mechanisms and these two processes are competitive and affected by the experimental conditions used.[160]

Using either diphenylphosphine or dicyclohexylphophine leading to the corresponding phosphines, Knochel et al. reported that catalytic amount of *t*-BuOK (20 mol%) in dimethyl sulfoxide (DMSO) allows the hydrophosphination of functionalized alkenes (equation 191).[161] The reaction of Cy_2PH with styrene produced phosphine oxide due to the sensitive intermediate dicyclohexylphosphine adduct oxidized by DMSO. The addition of Ph_2PH to *β*-methoxystyrene, elimination of methoxy, and subsequent oxidation by H_2O_2 produced the *trans*-alkenylphosphine oxide (equation 192).

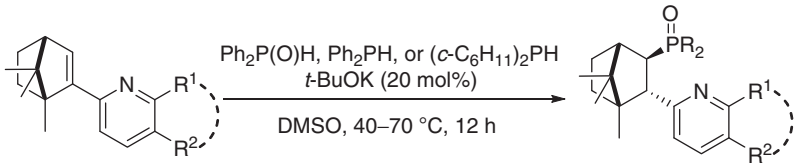


(191)



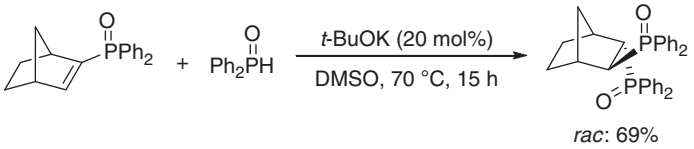
(192)

This method has been used to prepare new chiral P,N- and P,P-ligands from readily available chiral building blocks (equations 193 and 194).[162]



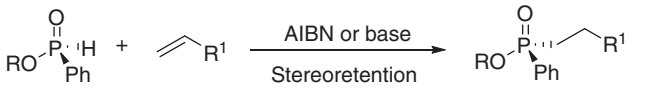
(193)

R = Ph; $R^1 = R^2 = H$; 87%
R = Ph; R^1 = Ph, R^2 = H; 72%
R = Cy; $R^1 = R^2 = H$; 55%
R = Ph; R^1-R^2 = CH-CH=CH-CH; 93%



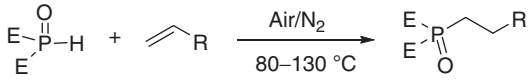
rac: 69% (194)

Han et al. reported stereospecific radical or base-catalyzed additions of the easily available (*R*p)-menthyl phenylphosphinate to alkenes, leading to a variety of functionalized optically pure (*R*p)-alkylphenylphosphinates in moderate to excellent yields (equation 195).[163]



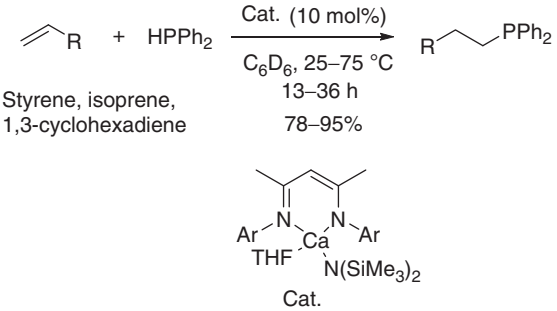
(*R*p) R^1 = alkyl, O, Si, S, P, Sn 49–97% (*R*p), R = (–)Menthyl (195)

Later, they found that a small amount of air (oxygen) can effectively initiate the addition of secondary phosphine oxides and H-phosphinates to alkenes (equation 196).[164] The author proposed that the addition probably proceeds via a radical chain mechanism.



E = Ph, *n*Bu
R = alkyl, CN, CO_2Et, O*n*-Bu, $P(O)R_2$ (196)

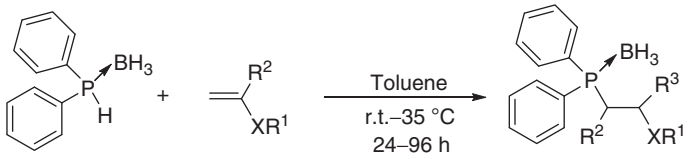
β-Diketiminato-stabilized calcium amide was an effective catalyst for the intermolecular hydrophosphination of a range of alkenes and alkynes (equation 197).[165] In this progress, a more electrophilic alkene would undergo polymerization to phosphine-terminated macromolecules.



Styrene, isoprene, 1,3-cyclohexadiene

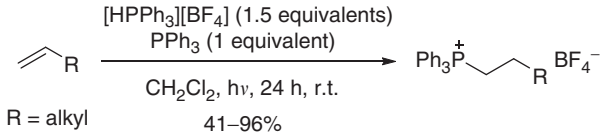
Cat. (197)

Vinyl ethers and vinyl thioethers are found to be reactive substrates for the addition reaction of phosphine-boranes to give the anti-Markovnikov adducts (equation 198).[166] These reactions occur under mild conditions without catalyst using phosphine-boranes as hydrophosphinating agents via a radical mechanism.



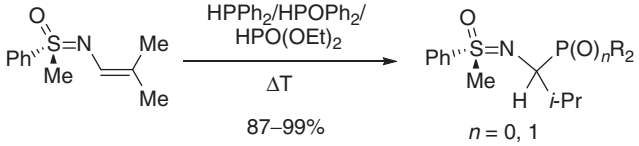
X = O, S
R^1 = Me, Et, Bu, Ph
R^2 = H, Me (198)

Grubbs et al. described the radical-mediated addition of triphenylphosphonium tetrafluoroborate to olefins to generate Wittig phosphonium salts.[167] This reaction can be performed using either standard radical initiators or photochemical conditions and was well applied to a range of olefins (equation 199).

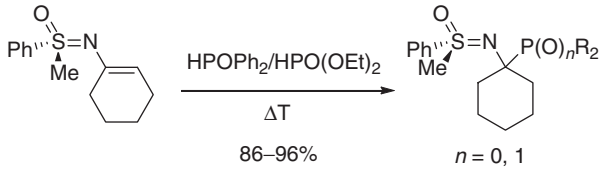


(199)

Gais et al. have shown that the *N*-vinyl sulfoximines undergo the noncatalyzed highly regioselective hydrophosphination and hydrophosphorylation with $HP(O)_n(R)_2$ to give the corresponding α-(*N*-sulfoximido) phosphines, phosphine oxides, and phosphonates in high yields (equations 200 and 201).[168]

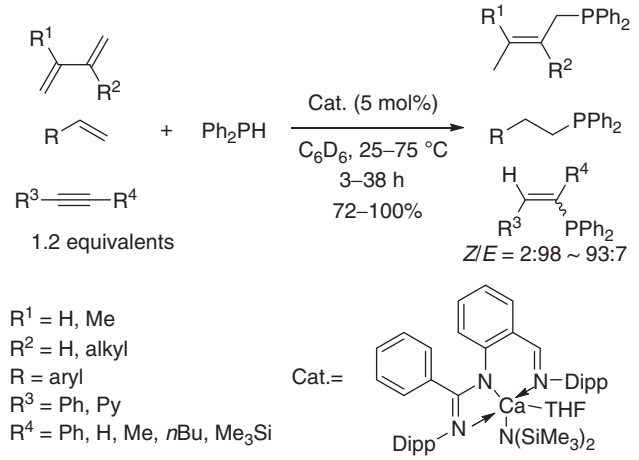


(200)



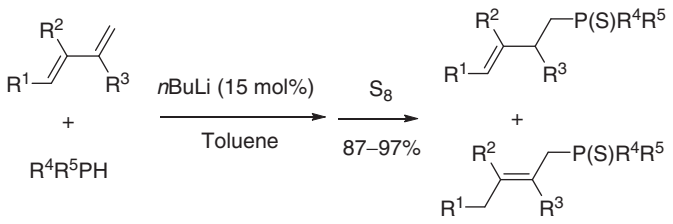
(201)

Cui et al. developed a calcium complex-catalyzed intermolecular hydrophosphination of alkenes, dienes, and alkynes with high activity and selectivity under mild conditions (equation 202).[169] Highly selective 1,4-additions for the examined conjugated 1,3-dienes has been observed.

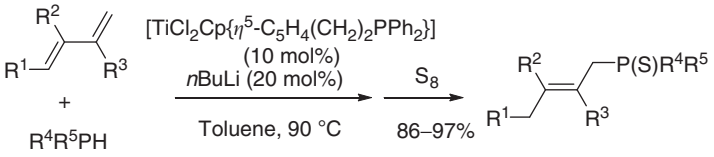


(202)

A simple and efficient base-promoted hydrophosphination of a variety of 1,3-dienes using several phosphanes has been developed by Gendre.[170] In all cases, the phosphorus atom of the reacting phosphane attacked the sterically less demanding side of the diene exclusively (equation 203). High regioselectivity toward 1,2- or 1,4-addition products was observed depending on the nature of the dienes. This procedure has also been applied to alkynes, unactivated olefins, and cyclo-1,3,5-heptatriene. A titanocene complex $[TiCl_2Cp(\eta^5\text{-}C_5H_4(CH_2)_2PPh_2)]$ was proved to be an efficient catalyst for the regioselective 1,4-hydrophosphination of 1,3-dienes (equation 204).[171] The coordinating phosphine on the titanium is believed to be responsible for the regioselectivity of the hydrophosphination.



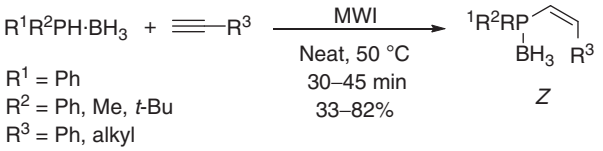
(203)



(204)

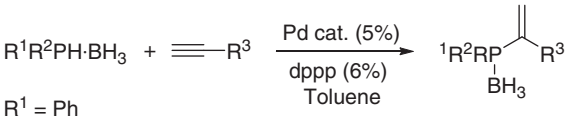
R^1 = alkyl
R^2 = alkyl, H
R^3 = alkyl, H
R^4 = Ph
R^5 = Ph, Me

Hydrophosphination of simple alkynes with secondary phosphine-borane reagents can provide a facile route for the construction of vinylphosphine derivatives. The reaction under thermal catalyst activation afforded the *Z*-*β*-adducts by regioselective attack of the phosphorus atom on the terminal carbon atom of the triple bond (equation 205).[172] In contrast, the reaction under metal catalyst activation afforded the *α*-adducts, indicating that the regioselectivity was independent of the nature of the catalyst (equation 206).[173]



(205)

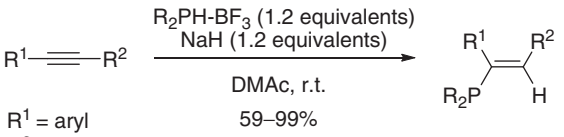
R^1 = Ph
R^2 = Ph, Me, *t*-Bu
R^3 = Ph, alkyl



(206)

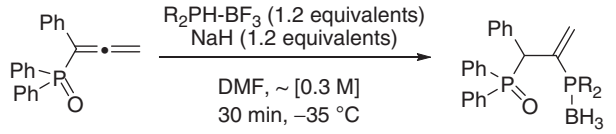
R^1 = Ph
R^2 = Ph, Me
R^3 = Ph, alkyl

Phosphine boranes were found to effectively hydrophosphinate internal, unactivated alkynes at room temperature under basic conditions without the need for catalysts or radical initiators.[174] Asymmetric hydrogenation of these species provided one of the shortest possible routes to chiral monodentate phosphines. In general, mixtures of *E*- and *Z*-olefins were obtained, with the *E*-isomer as the major isomer (equation 207). This method can be applied to hydrophosphination of allenyl phosphine oxides to prepare a wide variety of bis-phosphine derivatives (equation 208).



(207)

R^1 = aryl
R^2 = aryl, alkyl
R = Cy, Ph, *t*-Bu



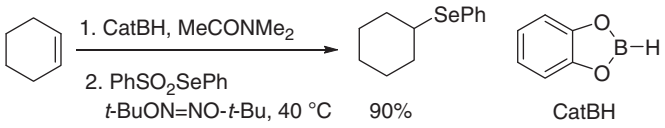
(208)

R = Ph, 82%
R = *m*-xyl, 83%
R = *c*-Hex, 66%
R = *p*-Tol, 84%

4.05.7 H–SeR Addition

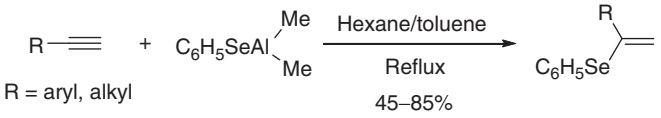
There are several reviews that summarize the advance in the addition of H–SeR to C–C multiple bonds.[175] However, only a few methods involve true electrophilic additions of selenols to C–C multiple bonds.

An efficient formal anti-Markovnikov addition of HSeR to olefins under mild reaction conditions is described by Renaud et al. (equation 209).[176] The procedure is based on the hydroboration of alkenes with catecholborane and subsequent selenation with $PhSO_2SePh$ via a radical process.



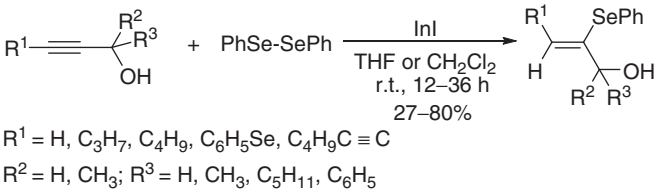
(209)

The dialkyl–phenylseleno–aluminum(III)-intermediated hydroselenation with alkynes gave the regiochemical production of the Markovnikov adduct (equation 210).[177] The aluminum phenylselenolates were generated and used *in situ* by the reaction of diphenyl diselenide with diisobutyl aluminium hydride.



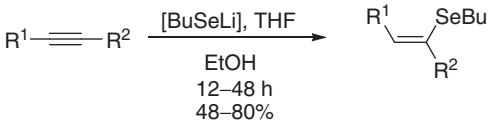
(210)

Peppe et al. explored an indium(I) iodide-promoted regio- and stereoseletive hydroselenation of 2-alkyn-1-ol derivatives with diphenyl diselenide to produce the Markovnikov adducts with stereochemistry corresponding to an *anti*-addition of the selenol constituents across the triple bond (equation 211).[178]



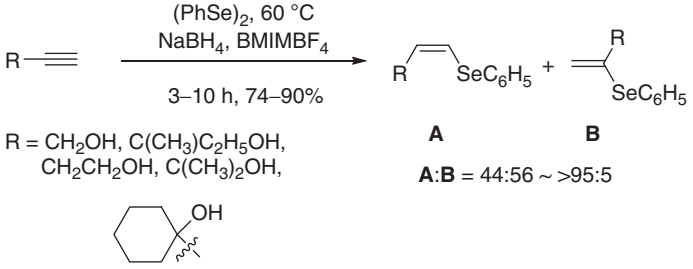
(211)

The hydroselenation of alkynes with lithium butylselenolate generated by reaction of *n*-butyllithium with elemental selenium was reported by Zeni et al. (equation 212).[179] The nature of the substituents (steric and electronic effects) on the triple bond played an important role in controlling the regio- and stereoselectivity.



(212)

Lenardão et al. described a new methodology of the addition of selenolate anions to alkynyl alcohols using recyclable ionic liquid as a solvent to give a mixture of vinyl chalcogenides (equation 213).[180]



(213)

4.05.8 Conclusions

Over the past 20 years, a remarkable number of new methods for the addition of H–X to C–C multiple bonds have been developed. This addition reaction provides one of the most atom-economical processes for the synthesis of functionalized molecules.

The addition of H–X (X = F, Cl, Br, and I) to alkenes, alkynes, and allenes has been extensively studied from both mechanistic and synthetic standpoints. The hydrogen halide generated *in situ* from the hydrolysis of various organic and inorganic halides was developed for regioselective addition to alkenes and alkynes under mild conditions, providing solutions to this challenging

procedure. A diversity of mechanisms appears to be involved in these processes. Electrophilic addition of hydrogen halides to carbon–carbon double and triple bonds is commonly observed following Markovnikov's rule. The nucleophilic addition of halide ion to electron-deficient alkenes and alkynes gave anti-Markovnikov products via a conjugate addition.

Aminomercuration–demercuration provided a very useful process for the addition of amines across unsaturated C–C bond in a regioselective manner under mild reaction conditions.[64] During recent years, hydroamination became a widely explored operation in the synthesis of nitrogen heterocylces and complex molecules.[74–77] The Markovnikov addition of protected amines to alkenes and alkynes has become a well-established synthesis strategy. More challenging and demanding further development is the conversion of strong basic amines, such as ammonia, as well as achieving adequate control of the regioselectivity in anti-Markovnikov fashion. The addition of amide to C–C multiple bonds can be achieved through the Ritter reaction. Similarly, $H–N_3$ addition to alkenes can be carried out directly.[89]

For the addition of H–O bond to alkenes and alkynes, synthetically useful protocols for Markovnikov hydrations, hydroalkoxylations, and hydrocarboxylations are available and find increasing applications in organic synthesis. However, there is a lack of methodology for regio- and stereoselective catalytic additions of water, alcohols, or carboxylic acids to unactivated alkenes and alkynes without metal catalysts; this issue has been partly addressed by application of metal catalyst.[181]

Radical addition of thiols to C–C multiple bonds is a basic and concise method to introduce sulfur atoms to organic molecules.[142] There is little work via an electrophilic pathway in accordance with Markovnikov's rule. In contrast to the reaction of alkenes, the addition of H–SR reagents to alkynes generally requires higher temperatures. The additions of phosphines to alkenes and alkynes have been studied and require either radical initiation or strong basic conditions. The mechanism may be either radical or ionic, depending on the nature of the substrate, irrespective of the experimental method used. The problem of the regio- and stereoselective addition of HSeR to alkynes is needed to be solved.[175] For more widespread applications, development of new catalyst system and a deeper understanding of the mechanistic details are required.

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4.06 Addition of X–Y Reagents to Alkenes, Alkynes, and Allenes

A Ogawa, Osaka Prefecture University, Sakai, Osaka, Japan

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Glossary

Aza-Bergman-type cyclization The cyclization reaction of 2-alkynylaryl isocyanides to form quinoline 2,4-biradical as key intermediates. Aza-Bergman-type cyclization provides quinoline derivatives conveniently.

Dichalcogenation Chalcogen elements mean sulfur, selenium, and tellurium. Therefore, dichalcogenation is a kind of addition reactions of such group 16 elements to unsaturated bonds to give vicinally dichalcogenated compounds directly.

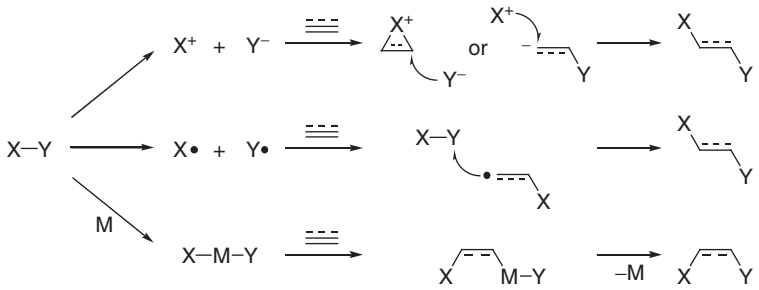
Electrophilic addition Addition reactions where heteroatom cationic species add to unsaturated bonds, followed by attack of nucleophiles. Asymmetric electrophilic addition is a synthetically useful tool to chiral compounds.

Hydrophosphination Addition reactions where phosphines add to unsaturated bonds to give vinylphosphines directly.

Interelement compound The compounds having heteroatom–heteroatom single bond involving group 13 (B), 14 (Si, Ge, and Sn), 15 (N, P, As, Sb, and Bi), 16 (O, S, Se, and Te), and/or 17 (F, Cl, Br, and I) elements. Interelement compounds are useful for introducing heteroatom groups into organic molecules.

4.06.1 Introduction

Addition reaction of heteroatom compounds bearing interelement linkage (X–Y) to carbon–carbon unsaturated compounds such as alkynes, allenes, and alkenes is one of the most useful and eco-friendly methods for selective introduction of heteroatom functional groups to organic molecules. Typically, three types of bond dissociation are considered, namely heterolytic bond cleavage, homolytic bond cleavage, and metal-catalyzed bond cleavage, and based on these bond dissociations, ionic, radical, and metal-catalyzed additions are expected to take place, as shown in Scheme 1.

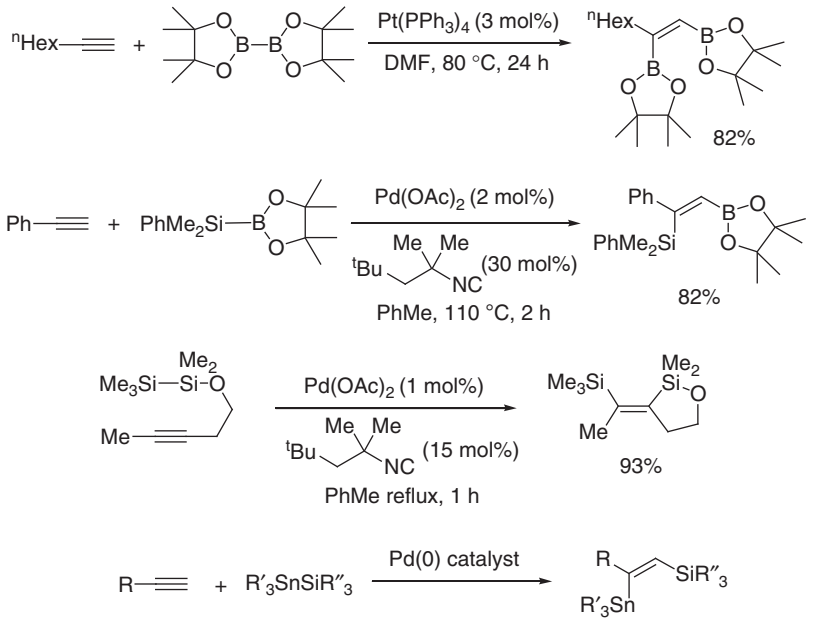


Scheme 1

Among these addition reactions, ionic addition reactions have been developed largely in the past century. Thus, a series of electrophilic addition reactions of X–Y reagents to carbon–carbon unsaturated compounds are representative examples and are very useful for the total synthesis of natural compounds and bioactive compounds.[1] Compared with ionic addition reactions, nonpolar addition reactions such as radical and metal-catalyzed addition of X–Y reagents to carbon–carbon unsaturated compounds had remained largely unexplored. In the past decade, however, a number of useful nonpolar addition reactions of several X–Y reagents to alkynes, allenes, and alkenes under radical conditions or in the presence of transition metal catalysts have been investigated.[2]

Therefore, the major focus in this chapter will be on the recently developed nonpolar addition reactions of X–Y reagents, i.e., radical additions and transition-metal-catalyzed additions. In addition, recent advance about ionic addition reactions of X–Y reagents to unsaturated bonds is also described.

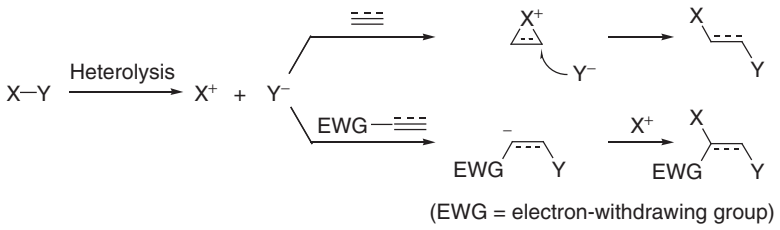
There are a variety of interelement compounds (X–Y reagents), which have a heteroatom–heteroatom single bond involving group 13 (B), 14 (Si, Ge, and Sn), 15 (N, P, As, Sb, and Bi), 16 (O, S, Se, and Te), and/or 17 (F, Cl, Br, and I) elements. Among these, the addition reactions of X–Y reagents having group 13 and/or 14 heteroatoms to carbon–carbon unsaturated bonds are dealt with in Chapter 4.16. These addition reactions generally proceed as catalytic reactions using transition metal complexes. Some representative examples of the transition-metal-catalyzed addition of B–B,[3] B–Si,[4] Si–Si,[5] and Si–Sn[6] reagents are shown in Scheme 2.



Scheme 2

4.06.2 Ionic Addition Reactions

In the past century, ionic addition reactions of X–Y reagents to alkenes, alkynes, and allenes have been growing and a variety of heteroatom functional groups are introduced to organic molecules efficiently by using these ionic addition reactions. In these ionic addition reactions, X–Y reagents dissociate heterolytically to generate X^+ and Y^-. Then, the former species act as electrophiles for carbon–carbon unsaturated compounds, whereas the latter ones act as nucleophiles for carbon–carbon unsaturated compounds, especially activated alkenes and alkynes such as enals, enones, and acetylene carboxylic acid derivatives (Scheme 3). Both reactions are usually promoted by using Lewis acids. In the nucleophilic addition, Lewis acid decreases electron density of carbon–carbon unsaturated bonds by coordination to electron-withdrawing group (EWG), and as the result, nucleophilic addition takes place easily.



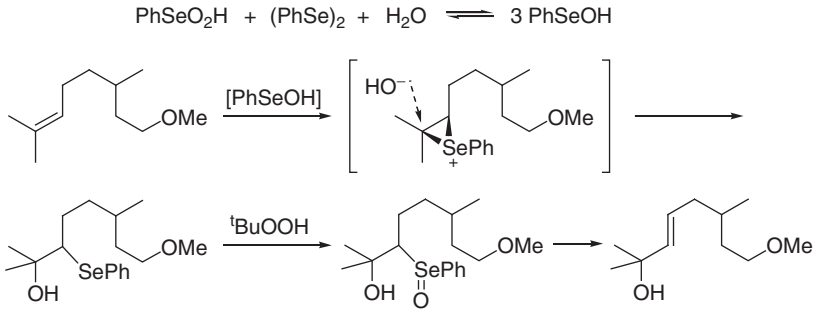
Scheme 3

4.06.2.1 Electrophilic Selenenylation of Alkenes

Representative X–Y reagents for electrophilic addition to alkenes and alkynes involve group 16 or group 17 heteroatom as an electrophile. For example, Cl_2 and Br_2 are well-known to be used as electrophiles for classical organic reactions, i.e., electrophilic

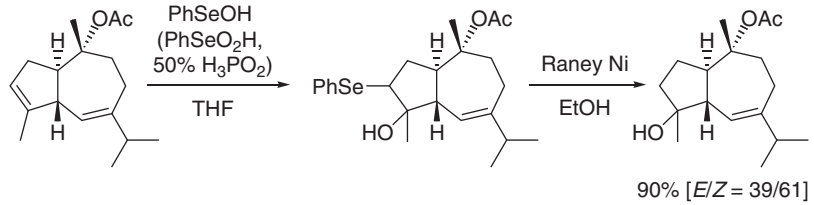
dihalogenation of alkenes and alkynes. Similarly, sulfenyl halides (PhS–Cl, PhS–Br), selenenyl halides (PhSe–Cl, PhSe–Br), selenenic acids (PhSe–OH, PhSe–O–SePh), and selenenamides (*N*-PSP (*N*-(phenylseleno)phthalimide)) are widely employed for electrophilic reactions to alkenes and alkynes.[7] In particular, selenenylating reagents are advantageous compared with sulfenylating reagents, because the introduced seleno groups are easily removed by oxidation via selenoxide *syn*-elimination or by reductive displacement with hydrogen on treating with tin hydride/2,2′-azobis(isobutyronitrile) (AIBN) or Raney nickel.

For example, benzeneselenenic acid can be conveniently generated *in situ* from benzeneseleninic acid, diphenyl diselenide, and water via comproportionation process, and then the subsequent addition to alkenes affords the corresponding *β*-hydroxy selenides, treatment of which with *t*-butyl hydroperoxide successfully leads to allylic alcohols via selenoxide *syn*-elimination process (Scheme 4).[8] In general, selenenylation reactions of alkenes proceed via the generation of seleniranium ion intermediates, resulting in *anti*-addition of seleno group and nucleophile.



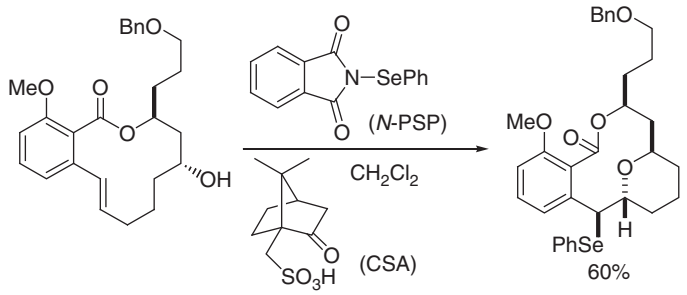
Scheme 4

In contrast to this oxidative treatment, reductive treatment of the *β*-hydroxy selenides with Raney nickel or tri(*n*-butyl)tin hydride/AIBN displaces the seleno group with hydrogen selectively. For example, electrophilic addition of selenenic acid to cyclopentene moiety is utilized as a key step for the first total syntheses of (+)-alismoxide and (+)-4-*epi*-alismoxide (Scheme 5).[9] In this reaction, benzeneselenenic acid is prepared by the reduction of benzeneseleninic acid with 50% H_3PO_2, and the introduced seleno group is removed reductively with Raney nickel.



Scheme 5

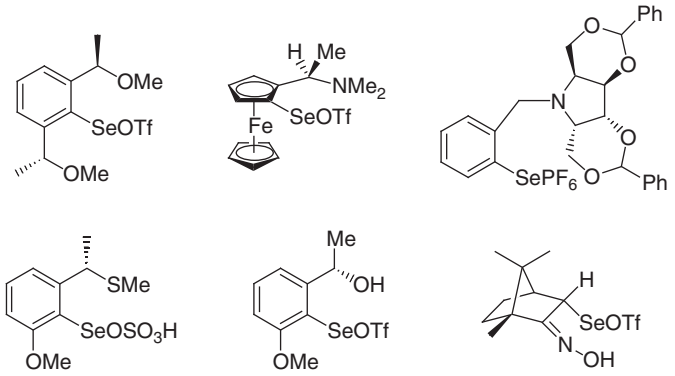
A representative application of the present electrophilic addition of selenenyl reagents is cyclofunctionalization reaction. For example, *N*-(phenylseleno)phthalimide (*N*-PSP) is well-known to be a useful reagent for cyclofunctionalization. Treatment of the 12-membered macrolactone with *N*-PSP affords the corresponding *trans*-pyran derivative selectively (Scheme 6).[10]



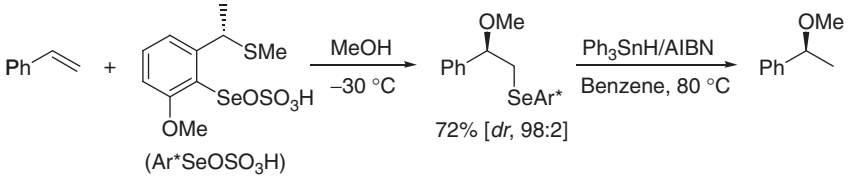
Scheme 6

Recently stereoselective selenenylation reactions of alkenes have been developed by using chiral selenenyl reagents. In general, chiral selenenyl reagents (R*SeX) are synthesized by the reaction of chiral diselenides (R*SeSeR*) with bromine to give chiral selenenyl bromides (R*SeBr), followed by treatment with AgX (X = OTf, OSO_3H, PF_6, ClO_4, etc.). Although chiral selenenyl

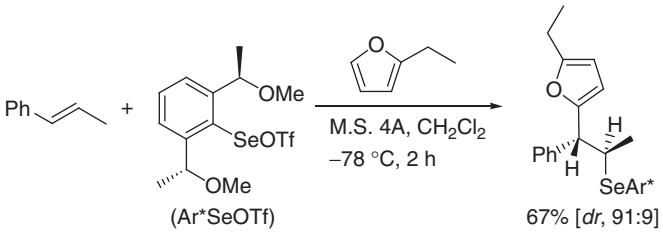
bromides (R*SeBr) can be used directly for asymmetric selenenylation of alkenes, less nucleophilic reagents such as R*SeOTf are usually employed for this purpose to avoid the nucleophilic attack by Br^-. Some representative chiral selenenyl reagents[11–16] are listed in Scheme 7. For example, asymmetric methoxyselenenylation of styrene takes place in methanol successfully by using chiral selenenyl sulfate (Scheme 8).[14a] Changing the solvent from methanol to CH_3CN/H_2O, asymmetric hydroxyselenenylation proceeds selectively (in the case of styrene, 65% yield, diastereomeric ratio (*dr*), 98:2). The seleno group (Ar*Se) of the products can be easily replaced by hydrogen on treatment with Ph_3SnH/AIBN. In place of oxygen-, nitrogen- and carbon-nucleophiles are employed for asymmetric selenenylation reactions of alkenes. Asymmetric carboselenenylation of (*E*)-β-methylstyrene with 2-ethylfuran proceeds diastereoselectively in the presence of chiral selenenyl triflate (trifluoromethanesulfonate) (Scheme 9).[11a]



Scheme 7

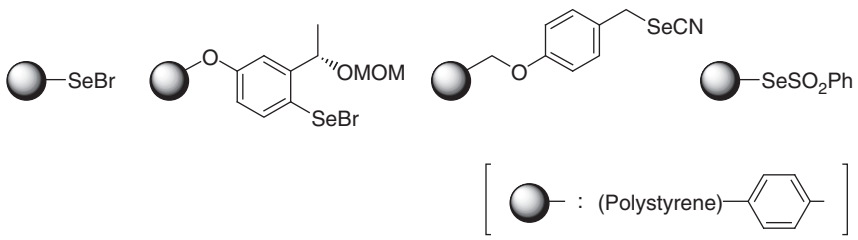


Scheme 8



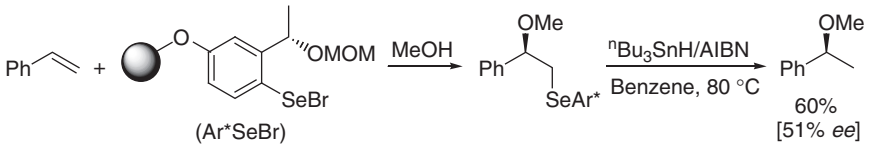
Scheme 9

In view of process chemistry, it is of great importance to recover and reuse selenenyl reagents. For this purpose, several polymer-supported selenium reagents have been developed (Scheme 10).[17–20] Asymmetric methoxyselenenylation of styrene in methanol



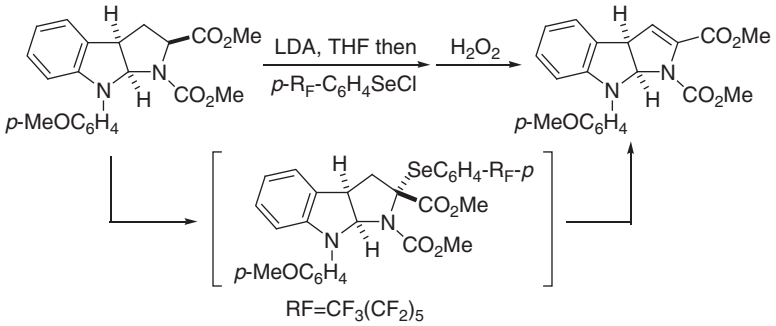
Scheme 10

is performed using polystyrene-supported chiral selenenylating reagent, and the following removal of the introduced chiral seleno group with tin hydride successfully affords the corresponding 1-methoxy-ethylbenzene stereoselectively (Scheme 11).[18]



Scheme 11

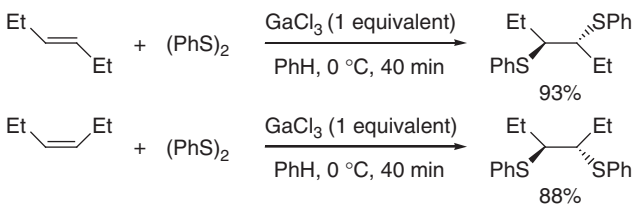
For the same purpose, electrophilic selenium reagents having fluorous tag such as *p*-C_6F_{13}–C_6H_4SeCl[21] and $C_8F_{17}SeCl$[22] have been also developed. Fluorous solvent such as FC-72 (a perfluorinated hydrocarbon solvent) forms different phase from organic and/or aqueous phase, and by using this property, fluorous compounds can be easily purified by extraction with fluorous solvent.[23] For example, a hexahydropyrroloindole derivative can be converted to the corresponding tetrahydropyrroloindole derivative via the reaction of the ester enolate with fluorous selenenyl chloride to give the α-selenoester, followed by oxidative elimination of selenium species on treatment with hydrogen peroxide (Scheme 12).[21] In this reaction, the resulting selenium species from the selenoxide elimination are easily reduced to fluorous diaryl diselenides on treatment with appropriate reducing agents such as sodium metabisulfite ($Na_2S_2O_5$). By continuous extraction with FC-72, the formed fluorous diaryl diselenides are then recovered in 95% yields.



Scheme 12

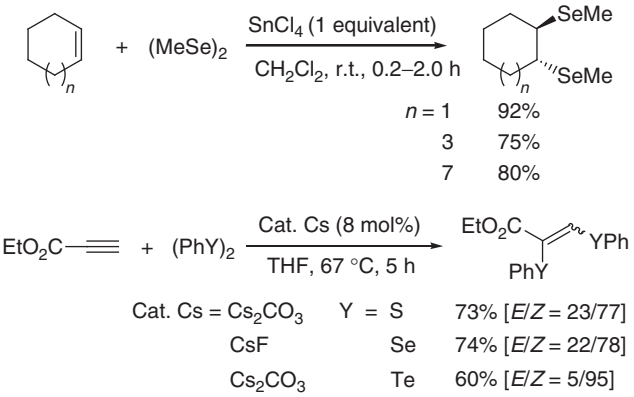
4.06.2.2 Lewis Acid-Promoted Addition of X–Y Reagents to Unsaturated Compounds

Addition of X–Y reagent to alkenes, alkynes, and allenes are useful for simultaneous introduction of two heteroatom functional groups with excellent regio- and/or stereoselectivity with atom-economy. For this purpose, radical and transition-metal-catalyzed addition reactions are widely employed in recent years (see Sections 4.06.3 and 4.06.4). As to ionic addition, conjugate addition of X–Y reagents to α,β-unsaturated carbonyl compounds are known to be classical organic reactions. However, examples of addition to unactivated alkenes are limited compared with radical addition and transition-metal-catalyzed addition. Recently, Lewis acid-promoted addition of X–Y reagents to unsaturated compounds are reported as useful pioneering works. For example, treatment of a mixture of organic disulfides and alkynes or alkenes with gallium trichloride affords the corresponding vicinally dithiolated adducts via highly selective *anti*-addition process (Scheme 13).[24] Boron trifluoride ($BF_3{\cdot}OR_2$) also effectively catalyzes *anti*-addition of organic disulfides to alkenes and conjugated dienes, leading to *vic*-1,2-dithioalkanes and 1,4-dithiolated conjugate addition products, respectively.[25] Similarly, hypervalent iodine(III) reagent (PhIO–TfOH) assists the dithiolation of alkenes to give the corresponding *trans* adducts in good yield.[26] Furthermore, addition of organic disulfides to alkynes, alkenes, and dienes is developed using electrochemistry.[27]



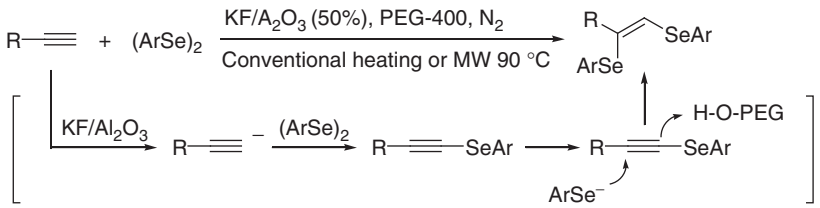
Scheme 13

Tin(IV) chloride induces the diselenation of alkenes and alkynes with dimethyl diselenide, affording the corresponding *trans* adducts selectively (Scheme 14).[28] In the case of diphenyl diselenide instead of dimethyl diselenide, the addition is ineffective. Cesium carbonate and fluoride catalyzes not only dithiolation but also diselenation and ditelluration of activated alkynes.[29]



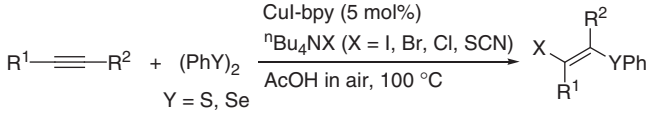
Scheme 14

Stereoselective diselenation of terminal alkynes with diaryl diselenides takes place on treating with KF/Al_2O_3, PEG-400 (Scheme 15).[30] The diselenation proceeds via the *in situ* formation of alkynyl selenides as intermediates, followed by formal *trans*-addition of selenols to the alkynyl selenides.



Scheme 15

When the reaction of organic disulfides or diselenides with alkynes is conducted in the presence of indium(I) iodide[31] or copper(I) iodide,[32] hydrothiolation or hydroselenation of alkynes takes place in preference to dithiolation or diselenation of alkynes. However, copper-catalyzed reaction of organic dichalcogenides with symmetrical internal alkynes in the presence of tetrabutylammonium halides leads to the halothiolation of the alkynes stereoselectively via *anti*-addition process in high yields (Scheme 16).[33] Although unsymmetrical aliphatic internal alkynes indicate no regioselectivities, halochalcogenation of aryl-substituted unsymmetrical alkynes such as 1-phenyl-1-propyne (R^1 = Ph and R^2 = Me) proceeds regio- and stereoselectively. The procedure can also be applied to introduction of thiocyanide group.

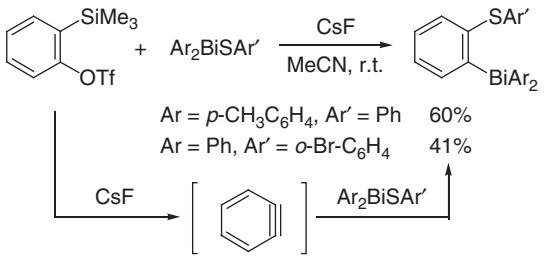


Scheme 16

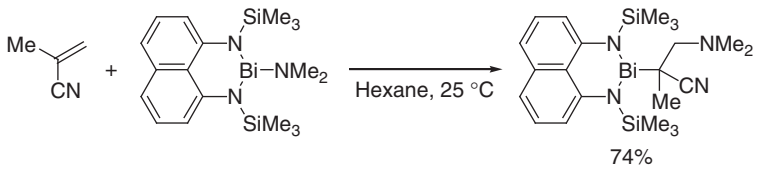
Reactions of tris(methylseleno)borane-$SnCl_4$ with alkenes give α,β-bis(methylseleno)alkanes, stereospecifically, and reactions with 1,3-dienes afforded α,δ-bis(methylseleno)alk-2-enes, regioselectively.[34] Similarly, the diselenation of alkynes with stannyl selenides in the presence of $SnCl_4$ is also reported.[35] (Arylthio)bismuthanes (Ar_2BiSAr'), which are synthesized by the reaction of Ar_2BiCl and Ar′SNa, react with benzyne to give *o*-(arylthio)phenyl bismuthanes in moderate to good yields (Scheme 17).[36]

Dimethylaminobismuth compounds add to electron-deficient alkenes and alkynes regioselectively to give β-(dimethylamino)-ethyl bismuth compounds (Scheme 18).[37]

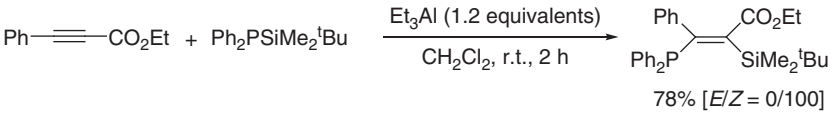
Lewis acid-induced reactions of silylphosphines with alkynes lead to the simultaneous introduction of two different heteroatom groups such as phosphino group and silyl group to alkynes with excellent regio- and stereoselectivity (Scheme 19).[38] Silylphosphines such as $Ph_2PSiMe_2{}^tBu$ are also reported to add to alkenes regioselectively in the presence of tetrabutylammonium fluoride.[39]



Scheme 17

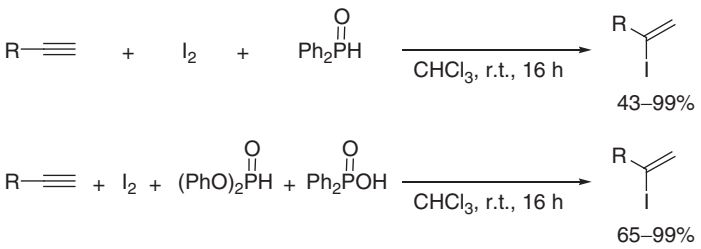


Scheme 18



Scheme 19

Markovnikov-type hydroiodination of terminal alkynes with iodine and $Ph_2P(O)H$ takes place selectively to afford the corresponding iodoalkenes regioselectively in good yields (Scheme 20).[40] After the reaction, $Ph_2P(O)H$ converts to $Ph_2P(O)P(O)Ph_2$, which finally changes to diphenylphosphinic acid ($Ph_2P(O)OH$) on treatment with oxygen and proton source. Combination of $(PhO)_2P(O)H$ and $Ph_2P(O)OH$ instead of $Ph_2P(O)H$ also provides the corresponding iodoalkenes regioselectively in excellent yields.[41] The procedures are applicable to a variety of alkynes such as functionalized terminal alkynes, internal alkynes, and silylalkynes. In the case of silylalkynes, desilylation also took place during the hydroiodination. The products, vinylic iodides, are useful precursors for transition-metal-catalyzed cross coupling reactions.



Scheme 20

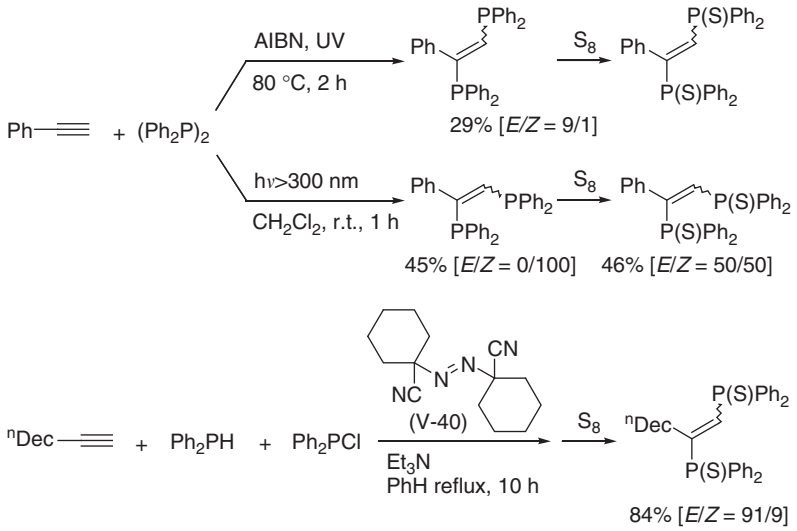
4.06.3 Radical Addition Reactions

4.06.3.1 Diphosphination of Alkynes and Related Addition Reactions

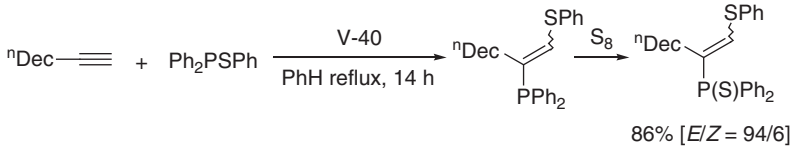
Diphosphines add to alkynes under radical conditions to give the corresponding vicinally diphosphinated alkenes, which can be isolated by treatment with elemental sulfur (Scheme 21).[42] It is convenient to prepare the diphosphines *in situ* from Ph_2PH and Ph_2PCl in the presence of Et_3N. In general, when radical initiators are used, *E*-isomers are obtained preferentially. However, photoinduced reaction leads to the formation of *Z*-isomers via photoisomerization from *E*-isomers.

Under similar radical conditions, thiophosphines having a P–S linkage add to alkynes regioselectively, as shown in Scheme 22.[43]

The combination of diphosphines and dichalcogenides is useful for the regioselective introduction of two different heteroatom groups to alkynes.[44] When a mixture of terminal alkynes, diphenylphosphine, and diphenyl disulfide are irradiated with the light

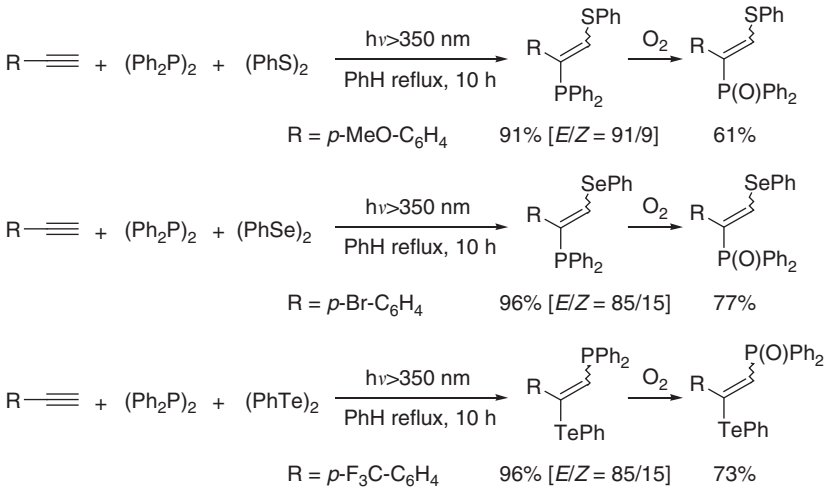


Scheme 21



Scheme 22

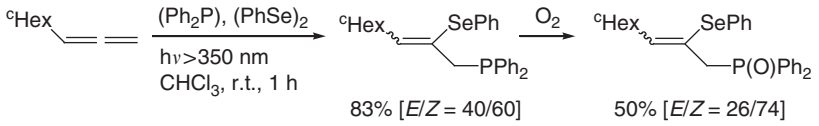
of wavelength more than 350 nm, regioselective thiophosphination of terminal alkynes takes place to give the corresponding 1-(phenylthio)-2-(diphenylphosphinyl)-1-alkenes after treatment with air. Similarly, in the case of diphosphine–diselenide mixed systems, seleno and phosphinyl group are introduced to the terminal and internal positions of alkynes, respectively, with excellent regioselectivity. In contrast, in the case of diphosphine–ditellurides mixed systems, different regioselectivity is observed, as shown in Scheme 23. These results suggest the relative reactivities of these heteroatom-centered radicals, i.e., PhS· > PhSe· > Ph2P· > PhTe·.



Scheme 23

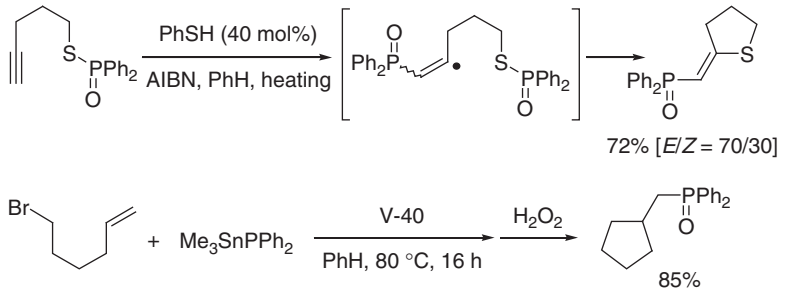
The present selenophosphination using the $(Ph_2P)_2/(PhSe)_2$ mixed system can be applied to allenes, and seleno group is introduced to the central carbon of allenes regioselectively, as shown in Scheme 24.[44b]

Radical cyclization reactions using interelement compounds containing phosphorus groups are developed, as shown in Scheme 25. Radical domino process relying on the homolytic cleavage of P–S bond allows the preparation of sulfur-containing



Scheme 24

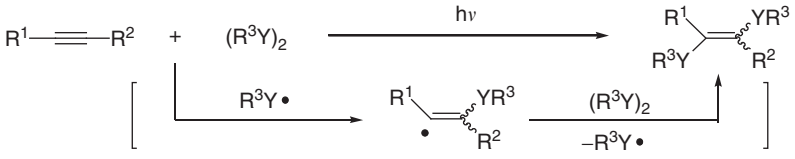
cyclic compound through addition of P-centered radical to alkynyl group and homolytic substitution on sulfur atom.[45] Furthermore, stannylphosphine is utilized for radical cyclization and phosphonation reactions of unsaturated halo compounds.[46]



Scheme 25

4.06.3.2 Dichalcogenation of Alkynes, Alkenes, Allenes, and Related Reactions

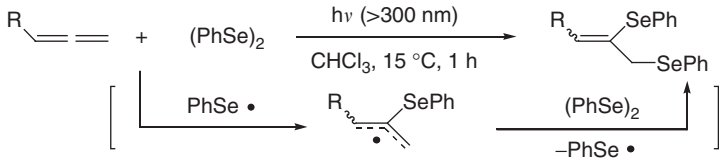
Organic dichalcogenides, i.e., disulfides, diselenides, and ditellurides, have their absorption maxima in ultraviolet (UV), near-UV, and visible regions, respectively (e.g., $\lambda_{max}=250$ nm ($(PhS)_2$); 340 nm ($(PhSe)_2$); and 406 nm ($(PhTe)_2$)). Therefore, on irradiation with these light sources, dichalcogenides undergo homolytic cleavage to generate the corresponding chalcogen-atom-centered radicals. In general, the chalcogen-centered radicals are less reactive compared with the oxygen-centered radicals, and cannot abstract allylic or propargylic hydrogen. Therefore, when the photoirradiation of organic dichalcogenides is conducted in the presence of alkynes, these dichalcogenides selectively add to alkynes by radical mechanism to form vicinal dichalcogenoalkenes (Scheme 26).[47] In the additions, *E*-isomers are generally obtained preferentially. The additions proceed via the formation of β-chalcogeno-substituted vinyl radical intermediates by attack of chalcogen-centered radicals to alkynes, followed by the S_H2 reaction of the vinyl radicals with organic dichalcogenides. The former step is considered to be a reversible process. Furthermore, recombination of the chalcogen-centered radicals takes place with the diffusion-controlled rate constant (approximately $10^{10}\ M^{-1}\ s^{-1}$) to reform the starting dichalcogenides. Therefore, the radical additions of organic dichalcogenides to alkynes generally require continuous photoirradiation and high concentration of the starting materials (the additions are usually conducted in the absence of solvent). In the case of ditelluration of alkynes,[48] the formed vicinal ditelluroalkenes are generally unstable on irradiation with near-UV light, and therefore, irradiation with the light of wavelength more than 400 nm is essential for this addition. Moreover, the radical additions of organic diselenides to alkynes proceed on heating to more than 140 °C in the dark.[49]



R^1 = Me	R^2 = H	R^3Y = MeS	UV light, 20 °C, 24 h	>80% [*E*/*Z* = 81/19]
^{n}Bu	H	PhSe	>300 nm, 40 °C, 24 h	91% [*E*/*Z* = 95/5]
Ph	H	^{n}BuSe	>300 nm, 40 °C, 24 h	83% [*E*/*Z* = 82/18]
Ph	^{n}Pr	PhSe	>300 nm, 40 °C, 24 h	69% [*E*/*Z* = 95/5]
^{n}Hex	H	PhSe	Dark, 150 °C, 10 h	74% [*E*/*Z* = 92/8]
^{n}Hex	H	PhTe	>400 nm, 40 °C, 96 h	62% [*E*/*Z* = 100/0]
Ph	H	PhTe	>400 nm, 40 °C, 3 h	73% [*E*/*Z* = 94/6]

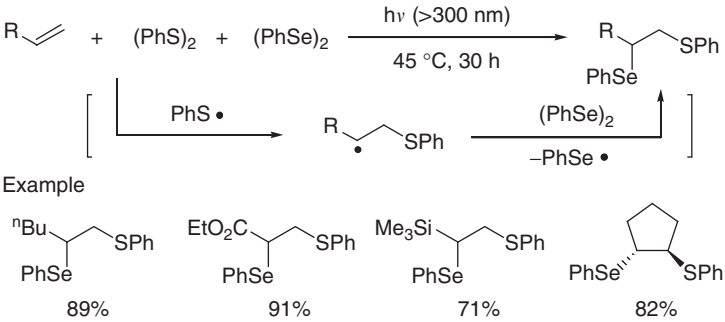
Scheme 26

As to the radical addition to allenes, photoinduced diselenation with organic diselenides takes place selectively at the terminal double bond efficiently, as shown in Scheme 27.[50] This addition may proceed through the formation of allylic radical intermediates by the attack of PhSe· at the central carbon of allenes, similarly as the radical addition of PhSeH to allenes. However, photoinduced reactions of allenes with organic disulfides result in polymerization of allenes, most probably due to the lower carbon radical capturing ability of organic disulfides. In the case of the photoinduced reactions of allenes with organic ditellurides, no reaction is observed, most probably owing to the instability of the allylic tellurides especially under photoirradiation conditions.



Scheme 27

In sharp contrast to the additions to alkynes, radical additions of organic dichalcogenides to alkenes are very inefficient reactions. For example, when the reactions of diphenyl disulfide and diselenide with 1-hexene are conducted under photoirradiation conditions, the desired vicinal addition products are obtained in only 7% (25 h) and 9% (32 h) yields, respectively. The addition rate constants of thio and seleno radicals are reported (e.g., for the addition to acrylonitrile, 4.6×10^5 M^{-1} s^{-1} (*p*-Cl-C_6H_4S·); 1.4×10^4 M^{-1} s^{-1} (PhSe·)), and thio radicals are more reactive than seleno radicals by a factor of approximately 10–50. However, the rate constants for the S_H2 reaction of alkyl radicals with $(PhSe)_2$ are known to be much larger than those with $(PhS)_2$ by a factor of approximately 160 (i.e. the rate constants for the S_H2 reaction of alkyl radical with diphenyl dichalcogenides are estimated to be 7.6×10^4 M^{-1} s^{-1} for $(PhS)_2$, 1.2×10^7 M^{-1} s^{-1} for $(PhSe)_2$, and 4.8×10^7 M^{-1} s^{-1} for $(PhTe)_2$, respectively). Based on these kinetic data, the difficulty of the radical addition of organic disulfides to alkenes is conceivably owing to the lower carbon radical capturing ability of disulfides. However, in the cases of organic diselenides and ditellurides, the lower reactivities of seleno and telluro radicals may contribute to the inefficiency of the radical addition of diselenides and ditellurides to alkenes. These considerations lead to the development of novel mixed systems of organic chalcogenides in the radical addition reactions. For example, the photoinduced reaction of various alkenes with $(PhS)_2$ and $(PhSe)_2$ proceeds smoothly to give the corresponding thioselenation products regioselectively (Scheme 28).[51]

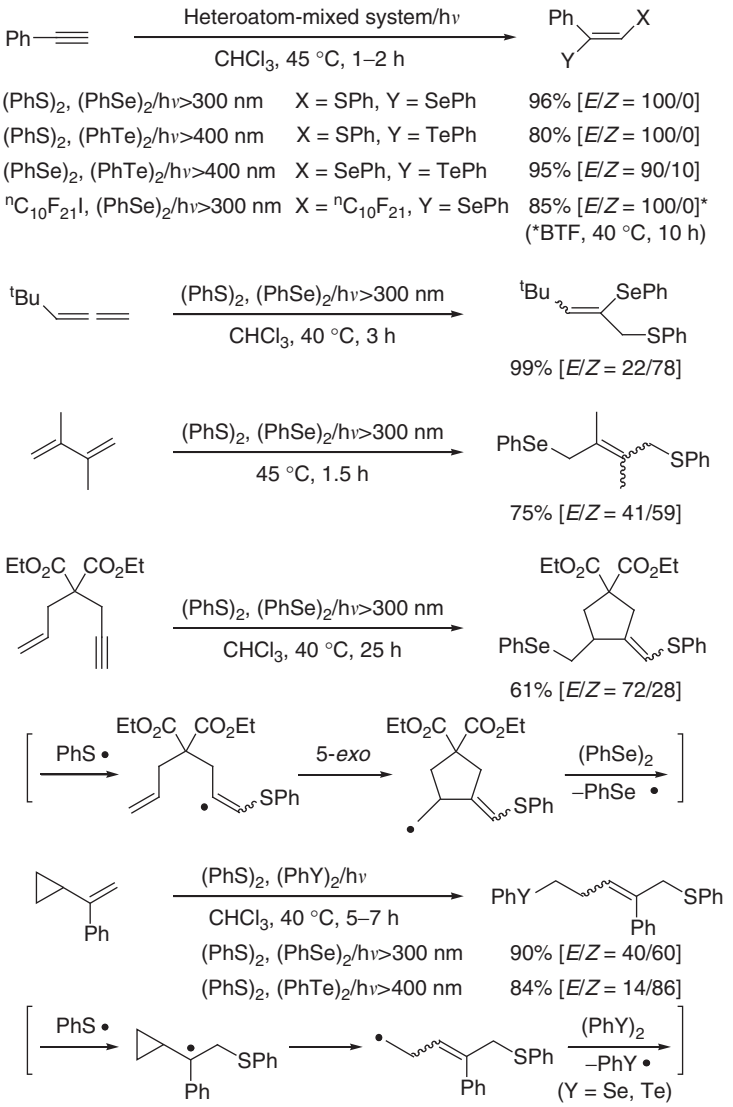


Scheme 28

This thioselenation using disulfide–diselenide mixed system can be applied to a wide range of carbon–carbon unsaturated compounds such as alkynes,[52] allenes,[53] conjugate dienes, enynes, and vinylcyclopropanes[54] (Scheme 29). In the case of enynes, the thioselenation proceeds via 5-*exo* cyclization process, whereas the thioselenation of vinylcyclopropanes occurs through ring-opening of cyclopropylcarbinyl radical intermediates.

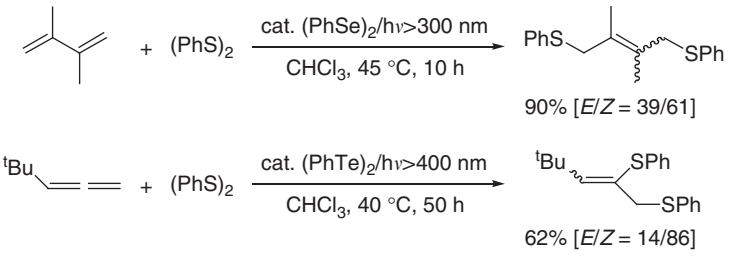
Furthermore, the present interelement compounds-mixed strategy can be applied to novel disulfide–ditelluride,[54] diselenide–ditelluride,[54] and diselenide–perfluoroalkyl iodide[55] mixed systems (Scheme 29). These mixed systems work well for the radical addition to alkynes, and the corresponding thiotelluration, selenotelluration, and perfluoroalkylselenation products are obtained regioselectively. In the cases of alkenes, thiotelluration and selenotelluration products are generally unstable under the photoirradiation conditions. Exceptionally, norbornene undergoes the photoinduced thiotelluration successfully. In addition, thiotelluration of vinylcyclopropanes proceeds smoothly to afford the ring-opening thiotelluration products.

Although the photoinduced reactions of disulfides with conjugate dienes or allenes afford polymerized products, interestingly, the copresence of diselenides or ditellurides in these systems leads to selective dithiolation of these unsaturated compounds (Scheme 30).[53,56] Combination of diselenide and elemental sulfur is employed for the sulfuration of dienes, which gives cyclic di- and tetrasulfides as main products.[57] This is because diselenides and ditellurides inhibit the unfavorable polymerization and *in situ*



Scheme 29

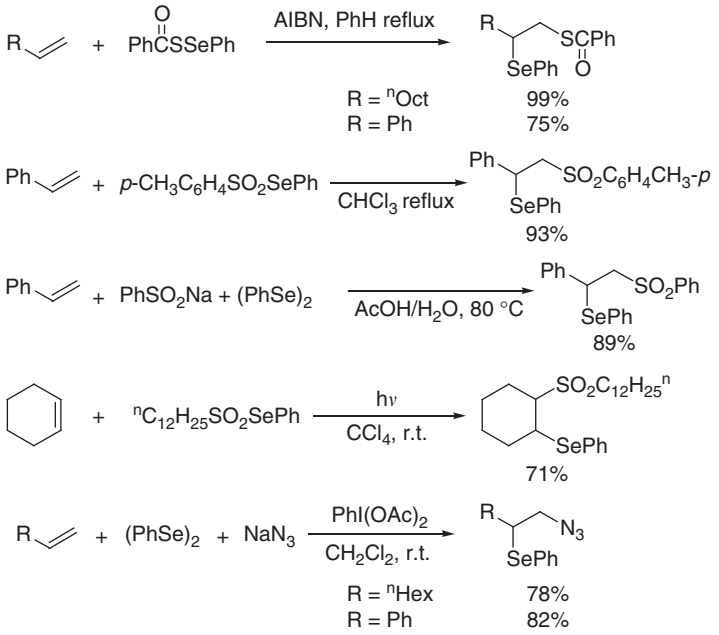
formed allylic selenides or tellurides easily convert to the corresponding sulfides under photoirradiation conditions. In sharp contrast, diphenyl diselenide is used as a chain transfer reagent for radical polymerization of methyl metharylate and styrene.[58]



Scheme 30

Simultaneous introduction of two different heteroatom functions involving group 16 elements by a radical mechanism is also demonstrated by selenothiocarboxylation,[59] selenosulfonation,[60] and azidoselenation,[61] as shown in **Scheme 31**.

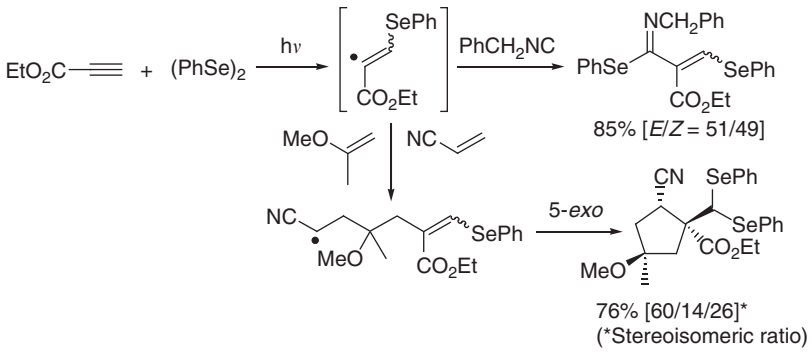
In these reactions, sulfur- or nitrogen-centered radical adds to the terminal position of alkenes and the subsequent S_H2 reaction with these interelement compounds affords the corresponding addition products with excellent regioselectivity. This selenosulfonation are applicable to alkynes, allenes, and vinylcyclopropane. In addition, free radical reaction of terminal acetylenes with



Scheme 31

sodium arenesulfinates and diphenyl diselenide in aqueous acetic acid affords (*E*)-*β*-(phenylseleno)vinyl sulfones, regio- and stereoselectively in high yields.[62]

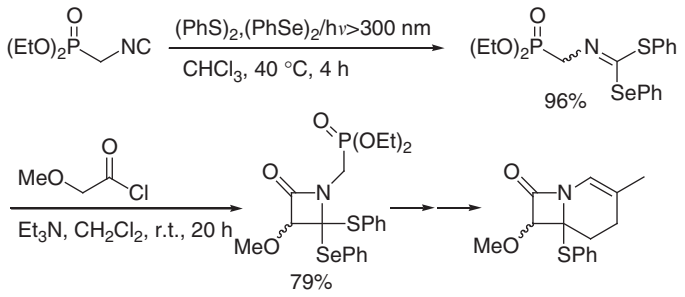
By using the excellent carbon radical capturing ability of diselenides, sequential addition reactions are attained, as shown in Scheme 32.[63] For example, seleno radical formed *in situ* adds to selectively to electron-deficient alkyne to generate *β*-seleno-vinyl radical as a key intermediate. In the presence of isocyanides, the photoinduced reaction of ethyl propiolate with $(PhSe)_2$ affords the three-component coupling product in good yield. In the copresence of electron-rich alkene and electron-poor alkene, sequential addition takes place and then, 5-*exo* cyclization and the following S_H2 reaction with diselenide afford the four-component addition/cyclization product selectively.



Scheme 32

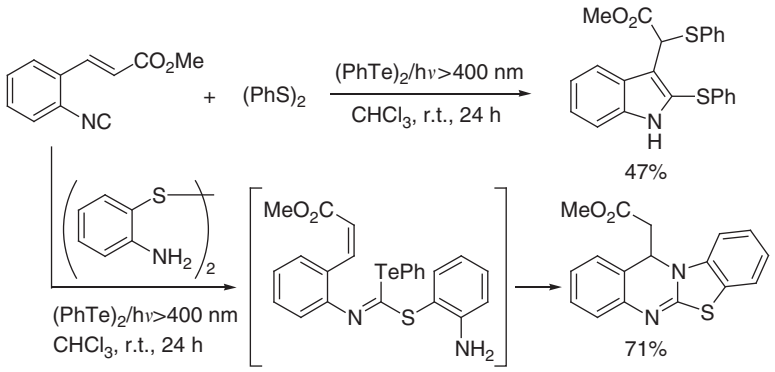
Isocyanides, which have a carbon–nitrogen multiple bond, also undergo the photoinduced thioselenation with organic disulfide and diselenide.[64] The reaction proceeds via the formation of imidoyl radical by the attack of thio radical to isocyanides (Scheme 33). The obtained thioselenation products can be employed as key precursors for the construction of *β*-lactam frameworks by the formal [2+2] cycloaddition with ketene equivalents. Scheme 33 indicates an example of the preparation of carbacephem derivatives by this thioselenation/[2+2] cycloaddition sequence.

Similarly, thiotelluration with disulfide–ditelluride mixed systems can take place only in the cases of isocyanides bearing EWG.[65] Because the thiotelluration products are relatively unstable compared with the thioselenation products, the thiotelluration products are in equilibrium with the corresponding imidoyl radical intermediates under photoirradiation conditions. Therefore, the thiotelluration reaction systems are useful for cyclization reactions. For example, methyl 2-(*o*-isocyanophenyl)acrylate reacts with $(PhS)_2$ in the presence of $(PhTe)_2$ under photoirradiation conditions to give the dithiolated indole derivative via radical cyclization of the imidoyl radical intermediates. However, when bis(*o*-aminophenyl) disulfide is employed in this reaction,



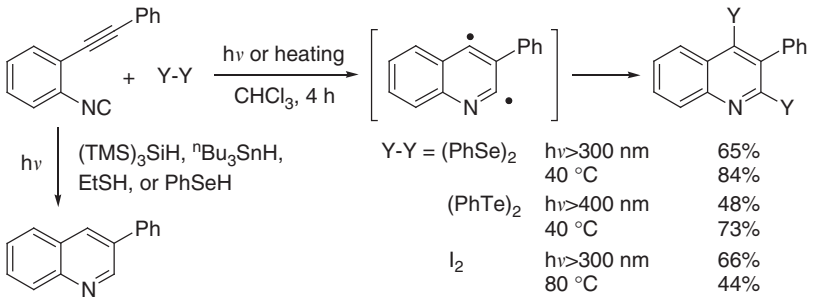
Scheme 33

substitution reaction of the PhTe group of imidoyl telluride intermediate by the amino group and Michael addition take place sequentially to afford the tetracyclic compounds in one portion (Scheme 34).



Scheme 34

In the case of *o*-alkynylaryl isocyanides, novel aza-Bergman-type cyclization takes place on photoirradiation or heating at 40–80 °C to form the corresponding biradical species, which are trapped with $(PhSe)_2$, $(PhTe)_2$, and I_2 to give the diselenolated, ditellurorated, and diiodinated quinoline derivatives successfully (Scheme 35).[66] When hydrogen sources such as tin hydrides, alkanethiols, and selenols are used instead of $(PhSe)_2$, $(PhTe)_2$, and I_2, dihydrogenated quinoline derivatives are obtained selectively. This result suggests the intermediacy of the biradical species. The obtained diiodinated quinoline derivatives, for example, are employed to be useful precursors for a series of cross coupling reactions.



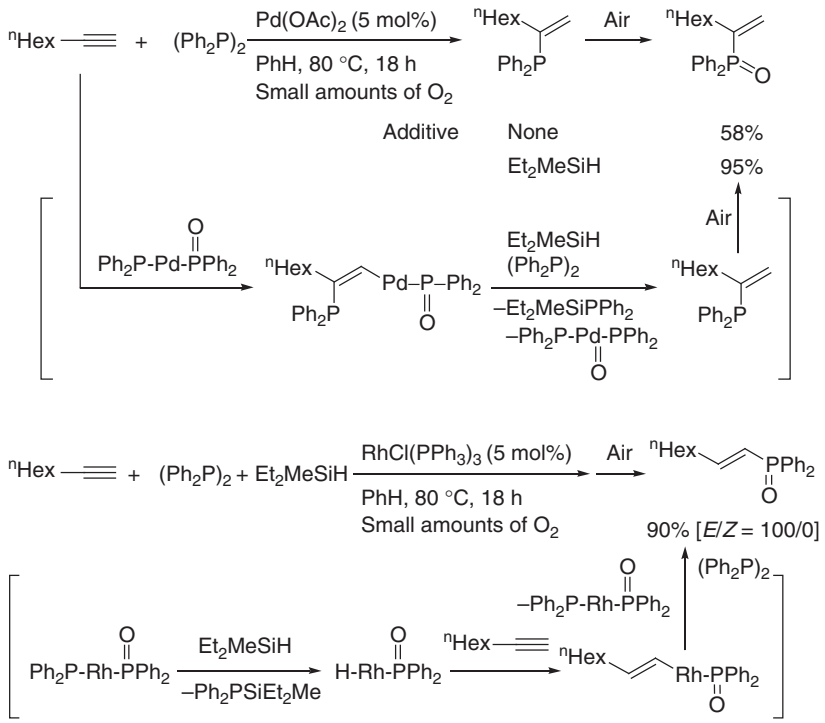
Scheme 35

4.06.4 Metal-Catalyzed Addition Reactions

4.06.4.1 Hydrophosphination of Alkynes and Related Unsaturated Compounds

In the presence of palladium catalyst, diphosphine can add to alkynes, but interestingly, the addition products are hydrophosphinated alkenes not diphosphinated alkenes (Scheme 36).[67] The experiment using a deuterized alkyne indicates acetylenic proton is the source of hydrogen. Thus, the use of hydrosilanes as hydrogen source leads to efficient hydrophosphination of alkynes, which affords the corresponding vinylphosphines regioselectively. This hydrophosphination requires the presence of

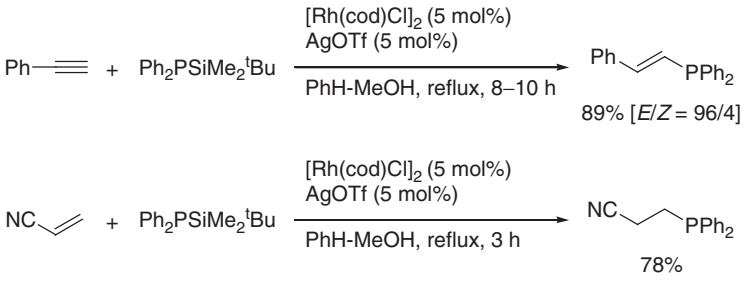
small amounts of oxygen, which oxidizes the diphosphine to its monooxide ($Ph_2P–P(O)Ph_2$). The *in-situ* formed diphosphine monooxide oxidatively adds to the low-valent palladium to generate $Ph_2P–Pd(II)–P(O)Ph_2$ species as the active catalyst. In the absence of oxygen, small amounts of vicinally diphosphinated alkenes are formed at the initial stage and they coordinate strongly to palladium catalyst to deactivate the catalyst.



Scheme 36

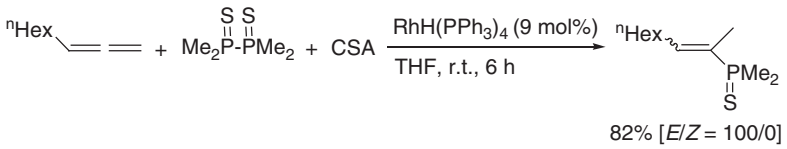
Under similar reaction conditions, changing the catalyst from the palladium complexes to Wilkinson's catalyst leads to the regiocomplement formation of vinylphosphines with excellent stereoselectivity ((*E*)-isomers are obtained exclusively).[68] In the case of palladium catalyst, the hydrophosphination may proceed via phosphinopalladation of alkynes by $Ph_2P–Pd–P(O)Ph_2$ species. However, the rhodium-catalyzed addition may take place via hydrorhodation of alkynes by $H–Rh–P(O)Ph_2$ species, which is formed by the reaction of $Ph_2P–Rh–P(O)Ph_2$ species with Et_2MeSiH.

A novel rhodium-catalyzed hydrophosphination of alkynes using a silylphosphine as a phosphino group source is reported, as shown in Scheme 37.[69] This catalytic reaction can be extended to hydrophosphination of activated alkenes such as acrylonitrile and ethyl acrylate.



Scheme 37

$RhH(PPh_3)_4$ catalyzes the reaction of tetraphenyldiphosphine with terminal alkynes in the presence of 2,4-dimethylnitrobenzene. However, this reaction does not afford the addition product but instead, 1-alkynylphosphines and their oxides are obtained as substitution products.[70] The same catalyst catalyzes the addition of diphosphine disulfide to allenes and the corresponding vinylphosphine sulfides are obtained in good yields (Scheme 38).[71]

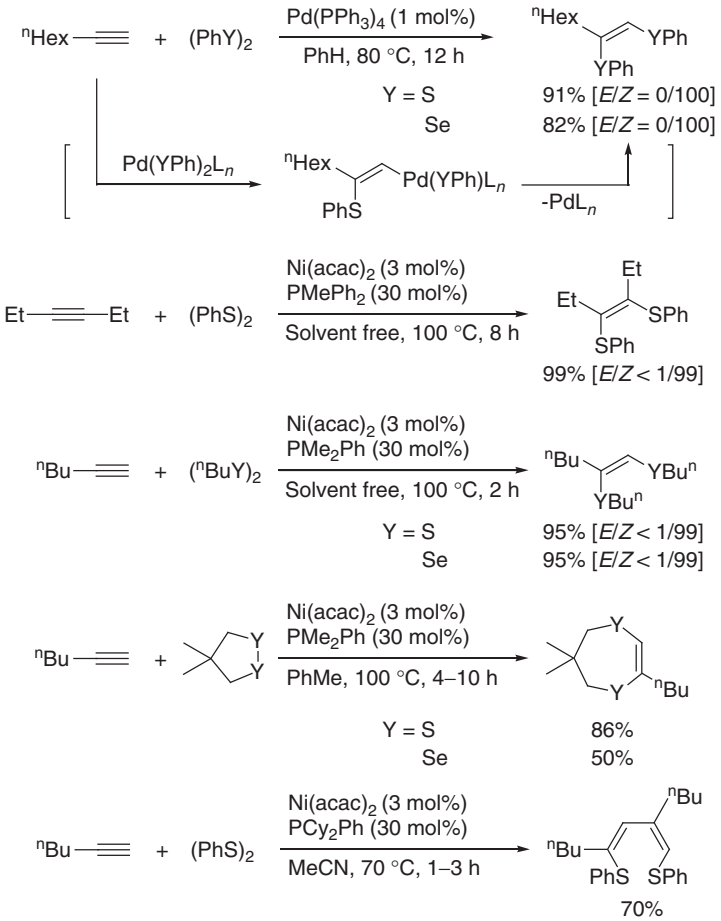


Scheme 38

4.06.4.2 Dichalcogenation of Alkynes, Alkenes, and Related Compounds

Although the utility of transition metal catalysts in various synthetic transformations using heteroatom compounds such as organic silicon, tin, and boron compounds is established, use of these catalysts for reactions of group 16 heteroatom compounds has remained largely unexplored. This might be partly due to the widespread prejudice that chalcogen compounds often bind strongly to the catalysts, thus poisoning them and making the catalytic reactions ineffective. During the past decade, however, a series of transition-metal-catalyzed reactions of chalcogen compounds have been developed.[72]

In the presence of tetrakis(triphenylphosphine)palladium(0), diaryl disulfides and diaryl diselenides add to terminal alkynes to afford the (*Z*)-1,2-bis(arylthio)- and (*Z*)-1,2-bis(arylseleno)alkenes, respectively, with excellent *E*-stereoselectivity (Scheme 39).[73] The reaction proceeds via the oxidative addition of the dichalcogenide to the palladium(0) catalyst to generate palladium sulfides species, regio- and stereoselective chalcogenopalladation of alkyne, and reductive elimination of the adduct from *β*-chalcogenovinylpalladium intermediate. Palladium-catalyzed dithiolation and diselenation of alkynes are also reported to take place in eco-friendly ionic liquid,[74] under solvent-free conditions,[75] or under microwave irradiation conditions.[76] Novel Ni(acac)$_2$–PMePh$_2$ (solvent-free) system is useful for stereoselective addition to internal alkynes.[77] The Ni(acac)$_2$–PMe$_2$Ph (solvent-free) system is also effective for the stereoselective addition of dialkyl disulfides and dialkyl diselenides to terminal alkynes.[78] Alternatively, the palladium-catalyzed addition of bis(triisopropylsilyl) disulfide ($^{i}Pr_3SiSSSiPr^{i}_3$) to alkynes to give (*Z*)-*vic*-bis(silylthio)alkenes. The subsequent desilylation with tetrabutylammonium fluoride (TBAF) and alkylation of the thus formed thiolate anions with alkyl iodide such as MeI successfully lead to the corresponding (*Z*)-*vic*-bis(methylthio)alkenes in good yields,

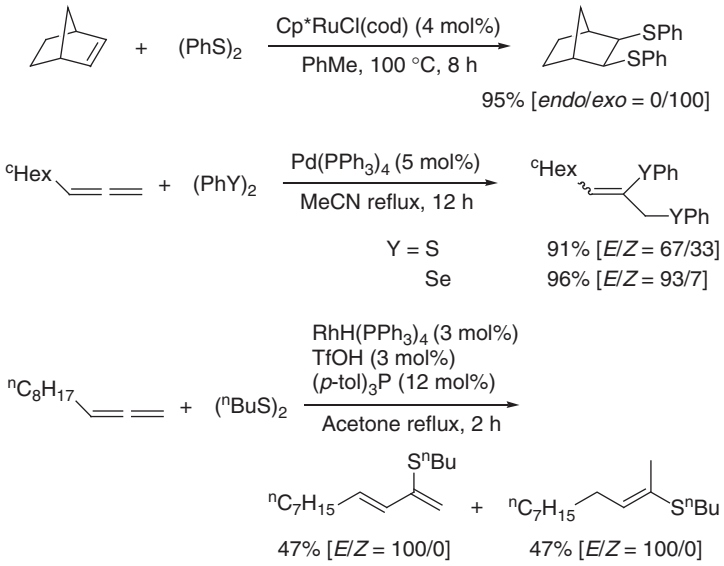


Scheme 39

stereoselectively.[79] Furthermore, cyclic disulfides and diselenides add to terminal alkynes in the presence of $Ni(acac)_2$–PMe_2Ph (or $Pd_2(dba)_3$–PCy_2Ph) catalyst.[80] Selection of phosphines as ligands lead to stereodefined synthesis of 1,3-dienes bearing terminal thio groups.[81]

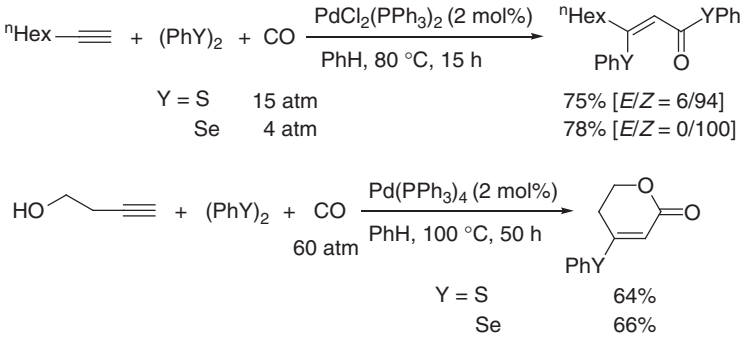
Several mechanistic studies are reported.[92,82] *In-situ* formed palladium sulfides and selenides undergo polymerization by coordination of chalcogeno groups to the palladium species intermolecularly and finally lose the catalytic activity.[92a,92b] The unfavorable polymerization of palladium chalcogenides species can be suppressed by the presence of alkynes, phosphines,[83] etc. In the case of more reactive nickel chalcogenides species, the size of the catalysts is well-controlled, and excellent catalytic activities are observed for a wide range of addition reactions of organic disulfides and diselenides to alkynes. In contrast, the corresponding transition-metal-addition of organic ditellurides to carbon–carbon unsaturated compounds does not proceed, owing to the rapid poisoning of the catalysts by the ditellurides.

Although $Pd(PPh_3)_4$ exhibits no catalytic activity toward the addition of disulfides to alkenes, Cp*RuCl(cod) exhibits an excellent catalytic activity toward the desired bisthiolation of alkenes (**Scheme 40**).[84] In the presence of palladium(0) catalyst, diaryl disulfides and diselenides add to allenes regioselectively at the terminal double bond to give the corresponding vicinally dichalcogenated products in good yields.[85] However, when $RhH(PPh_3)_4$ is used as the catalyst, hydrothiolation products are obtained selectively.[86]



Scheme 40

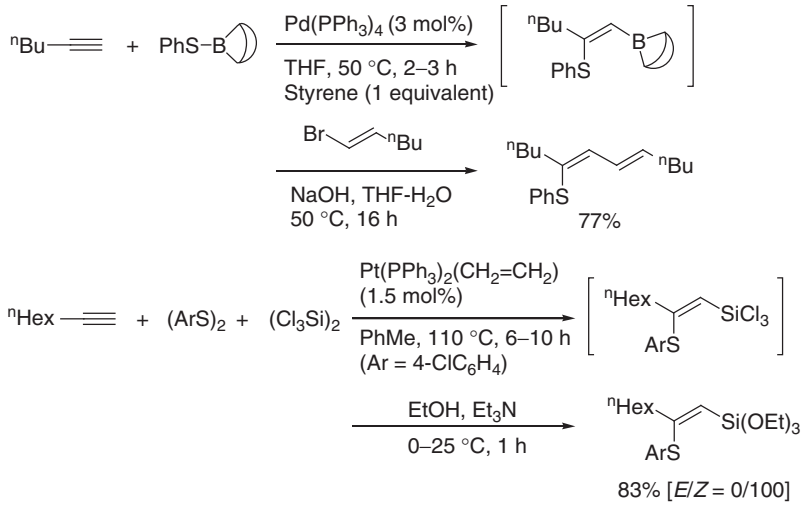
When the $Pd(PPh_3)_4$-catalyzed reactions of terminal alkynes with diaryl disulfide or diaryl diselenide are conducted under pressurized carbon monoxide, carbonylative thiolation or selenation proceeds regioselectively, as shown in **Scheme 41**.[73a,b] The present palladium-catalyzed carbonylation with diaryl dichalcogenides and CO is applied to propargyl alcohols, and β-(arylchalcogeno)-α,β-unsaturated lactones are obtained via intramolecular cyclization.[87]



Scheme 41

Transition-metal-catalyzed addition reactions of heteroatom compounds bearing interelement linkages such as group 13–group 16, group 14–group 16, group 15–group 16, and group 16–group 16 to alkynes are reported. For example, 9-(phenylthio)-9-borabicyclo[3.3.1]nonane, which has a group 16–group 13 interelement linkage, adds to terminal alkynes in the presence of Pd

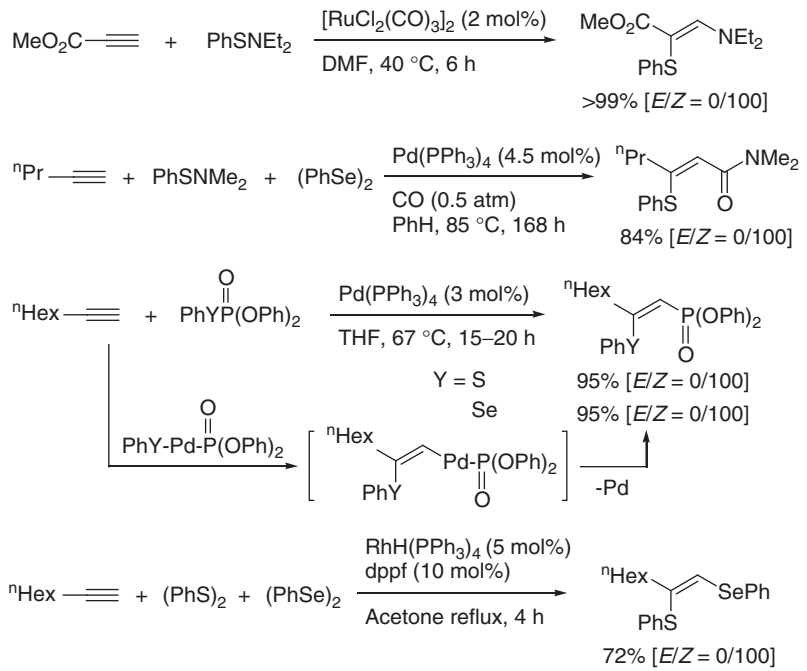
$(PPh_3)_4$, and the corresponding β-(phenylthio)alkenylboranes are obtained regio- and stereoselectively. The subsequent palladium-catalyzed cross-coupling of the thus formed alkenylboranes with organic halides leads to the regio- and stereoselective synthesis of vinyl sulfides (Scheme 42).[88]



Scheme 42

The palladium-catalyzed addition of a group 14–group 16 interelement linkage such as $PhSeYMe_3$, (Y=Si and Ge) and $Y(GeMes_2)_2$ (Y=S and Se) to alkynes (RC≡CH) was also examined, and the corresponding addition products are obtained regio- and stereoselectively in relatively low yields (e.g., (*Z*)-R(PhSe)C=CH($GeMe_3$), 35%).[89] $Pt(PPh_3)_2(CH_2=CH_2)$ is shown to catalyze the regio- and stereoselective thiosilylation of alkynes with $(ArS)_2$ and $(Cl_3Si)_2$ (Scheme 42).[90]

As to the heteroatom compounds bearing a group 15–group 16 interelement linkage, sulfenamides are reported to add to alkynes regio- and stereoselectively in the presence of ruthenium catalyst (Scheme 43).[91] $Pd(PPh_3)_4$ catalytically assembles sulfenamides, terminal alkynes, carbon monoxide, and diphenyl diselenides regio- and stereoselectively in a single-pot reaction to produce good yields of β-(phenylseleno)-acrylamides.[92] Moreover, PhS–P(O)$(OPh)_2$ and PhSe–P(O)$(OPh)_2$, undergo insertion of alkynes regio- and stereoselectively in the presence of $Pd(PPh_3)_4$.[93]



Scheme 43

In the presence of $RhH(PPh_3)_4$ catalyst, terminal alkynes undergo thioselenation with $(PhS)_2$ and $(PhSe)_2$ to give 1-(phenylseleno)-2-(phenylthio)alkenes preferentially.[94]

In conclusion, this chapter describes recent advance of addition of X–Y reagents to unsaturated compounds. In addition to ionic addition, which has been developed extensively in the past three decades, radical addition and transition-metal-catalyzed addition have been investigated recently. These three addition methods, i.e., ionic, radical, and transition-metal-catalyzed addition reactions, are complementary with each other, and attain regio- and/or stereoselective synthesis of a wide variety of heteroatom compounds, which are useful synthetic intermediates as well as bioactive compounds and functional materials. Therefore, a series of methods mentioned here are expected to open up new fields of heteroatom compounds in materials science, biochemistry, and organic synthesis.

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4.07 Electrophilic Cyclization

X Jiang and H Liu, East China Normal University, Shanghai, People's Republic of China

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Glossary

π-Acid π-Acid is a kind of Lewis acid that could accept electrons from Lewis base via antibonding π-orbitals.

Electrophile Electrophile is the molecule or ion that is electron deficient and in some way could accept a pair of electrons to make a new covalent bond. Electron deficiency would include a formal positive charge or a partial positive charge. 'E' and 'E^+' are common abbreviations for generic electrophiles. The common electrophiles include X_2, X^+, RS^+, RSe^+, H^+, Lewis acid, and so on.

Halolactonization It is the reaction to form a lactone by the addition of halogen and oxygen in carboxylic acid or carboxylate across a carbon–carbon double bond.

Nucleophile Nucleophile is the reactant that provides a pair of electrons to form a new covalent bond. A nucleophile that shares an electron pair with a proton is usually called a Brønsted–Lowry base, or just a base. The common nucleophiles include carboxylic acid, carboxylate, hydroxyl, amino, carbonyl oxygen, carbon, as well as thiol.

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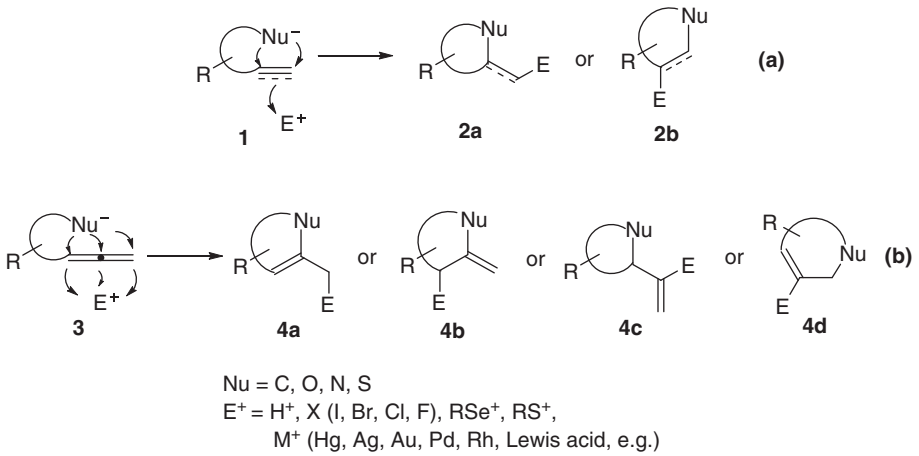
4.07.1 Introduction

4.07.1.1 Coverage

Electrophilic cyclizations are those reactions that involve the interaction of the electrophilic reagent to alkenes, alkynes, allenes, conjugated dienes, and other carbon–carbon multiple bonds, although followed by a subsequent intramolecular addition of an internal nucleophile (Scheme 1). These processes generate carbocycles from carbon-centered nucleophiles and heterocycles from heteroatom-centered nucleophiles, such as carboxylic acid, carboxylate, hydroxyl, amino, carbonyl oxygen, as well as thiol.

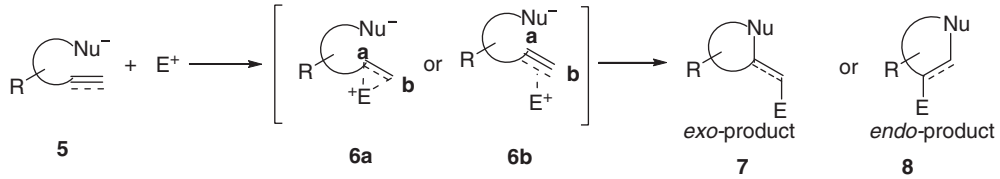


Scheme 1 Concept of the electrophilic cyclization.

Electrophilic cyclization was first reported by Bougault in 1904; it was about iodocyclization of unsaturated acids.[1] Since then, this type of reaction has undergone incredible growth, especially over the past decades. There have been numerous examples of synthetic application of electrophilic cyclizations, and a large number of reviews on this subject have appeared.[2] Therefore, only the most relevant achievements and synthetically useful electrophilic cyclization reactions after 1991 will be covered in this chapter. The sections of this chapter are summarized according to the type of electrophilic reagents, such as halocyclization, sulfenylcyclization, and selenocyclization; some metallic reagent-mediated reactions such as mercury-, gold-, silver-, and platinum-catalyzed electrophilic cyclization have also been discussed.

4.07.1.2 Mechanism

The general mechanism of electrophile-initiated cyclofunctionalization is shown in Scheme 2. First of all, the electrophile interacts with unsaturated carbon–carbon π-system **5** to generate activated intermediates cyclic 'onium' ion **6a** and/or the π-complex **6b**.[2k] Both intermediates **6a** and **6b** have two reactive centers **a** and **b**. Then nucleophilic *anti* attack of the nucleophile on the activated intermediate **6a** or **6b** generates two regioselective products: *exo*-product **7** or *endo*-product **8**.



Scheme 2 Mechanism of the electrophilic cyclization.

4.07.1.3 Baldwin's Rules for Ring Closure

'Baldwin's rules' historically have served as one of the most useful tools in the arsenal of synthetic organic chemists.[3] Not only have they defined the nomenclature and the vocabulary for describing and classifying ring-closure steps, but it also combined the existing empirical knowledge with basic stereoelectronic considerations to predict the favorable modes of cyclization.

Baldwin's rules classify ring closures based on three factors: (1) the ring size being formed (indicated through a numerical prefix), (2) the position of the breaking bond that has to be broken in the cyclization, relative to the forming ring (*exo*, in which the breaking

bond is external to the newly formed ring, and *endo*, in which the breaking bond is within newly formed ring), and (3) the hybridized state of the carbon atom undergoing the ring-closing reaction (sp = **dig**onal, sp^2 = **trig**onal, and sp^3 = **tet**rahedral).

Baldwin summarized the relative nature of ring formation involving three- to seven- membered rings as either favorable or unfavorable.[3a,4] These terms are not meant to describe the absolute probability that a reaction will or will not take place, but rather are used in a relative sense.

4.07.2 Halocyclization

Halocyclization is a powerful tool to construct rings by the addition of a nucleophile and halogen atom across unsaturated bonds. Oxygen-, nitrogen-, sulfur-, selenium-, halogen-, and carbon-centered nucleophiles are widely used in halocyclization reactions. Not only iodine, bromine, chlorine, and fluorine but also electrophilic halogen reagents such as IOAc, *N*-iodosuccinimide (NIS), NBS, NCS, ICl, IBr, $I(collidine)_2PF_6$, $Br(collidine)_2PF_6$, $I(collidine)_2ClO_4$, and Barluenga's reagent (IPy_2BF_4) have been successfully used in halocyclization. Hypervalent iodine(III) compounds are also considered as efficient electrophiles. This section discusses the halocyclization reactions by various electrophilic halogen reagents.

4.07.2.1 Iodocyclization

Iodolactonization reactions are a well-known process to obtain rings (3–7). The lack of regioselectivity and slow reaction rates are the reasons why this methodology has been rarely used for medium and large macrolactones (≥ 8). Anyway, since the iodolactonization reaction was first reported by M. J. Bougalt in 1904, it has become one of the most effective protocols to synthesize lactones, which is widely applied in syntheses of many biologically important natural products.[1,2] A large number of works dealing with iodolactonization reaction have been reported, and many comprehensive reviews have been presented.[2h,2i,2f,2m,5] Although halogen molecules are nonpolar, they are easily polarized by the interaction with unsaturated C–C bonds. The electrophilic properties of iodine have been exploited over one century, and the use of molecular iodine as an inexpensive, nontoxic, and readily available electrophilic reagent has now received considerable attention in organic synthesis.[2j,6] Not only was iodine molecule used as the electrophile, but a variety of new iodination reagents have also been developed, such as IOAc, NIS, ICl, IBr, and some hypervalent iodine(III) compounds.

4.07.2.1.1 Oxygen nucleophiles

4.07.2.1.1.1 Cyclization involving alkenes

Oxygen nucleophiles have been extensively applied in cyclocyclization reactions. Some examples of nucleophiles with functional groups containing oxygen are shown in Figure 1.

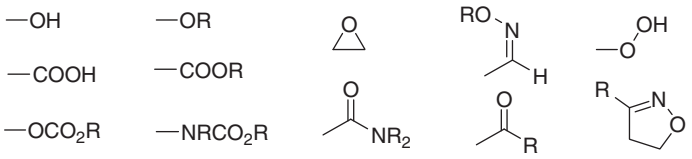


Figure 1 Oxygen nucleophiles.

Iodine-initiated cyclization of substrates with unsaturated bond is used extensively in the synthesis of oxygen heterocycles; in this chapter some representative examples and leading references will be described. Iodocyclizations of the homoallylic alcohols proceed with excellent stereoselectivity, generating tetrasubstituted tetrahydrofurans (THFs) in anhydrous MeCN (Scheme 3).[7] This reaction follows antiaddition to give stereospecific products in high yields.

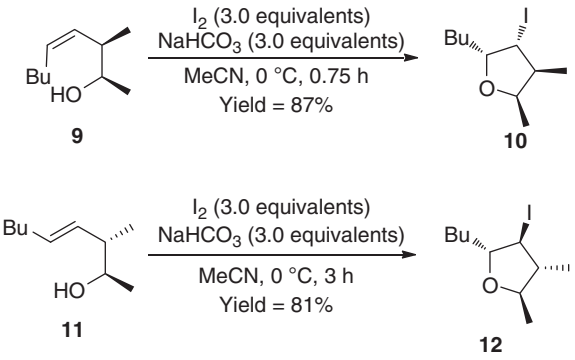
Then 5-*endo-trig* iodocyclizations of homoallylic alcohols generate *β*-iodotetrahydrofurans in highly efficient and stereoselective manner in anhydrous MeCN with $NaHCO_3$ as the base (Scheme 4).[8] Such cyclizations are exceptional cases to Baldwin's rules. They undergo well-ordered chair-like transition states (**14** or **17**) basing on the electrophile-driven to give 5-*endo-trig* cyclization product.

Another example shows that tetrasubstituted THFs can be obtained from readily available homoallylic alcohols in excellent yields in the presence of I_2 and AgTFA via a very unusual 5-*endo* cyclization (Scheme 5).[9]

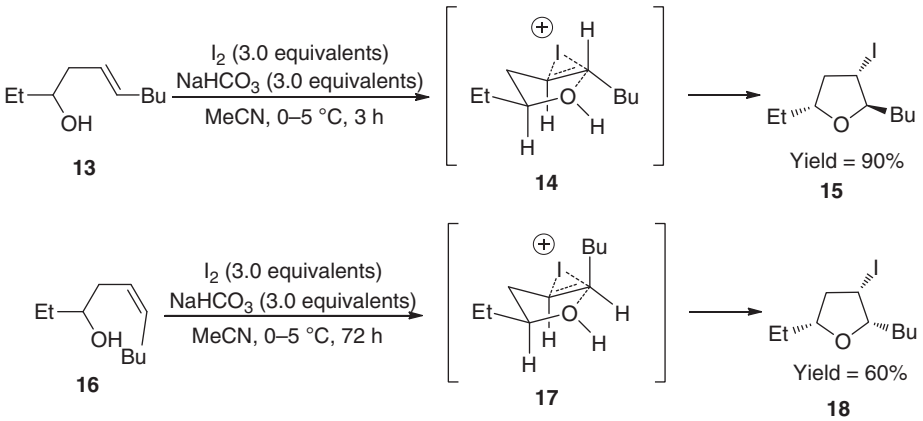
The iodocyclization reactions of cyclohexa-1,4-diene derivatives containing chiral tether inducing high levels of diastereocontrol have been investigated, which is the desymmetrization of cyclohexa-1,4-diene (Scheme 6).[10]

To extend the methodology of I_2-induced cyclization of 2-alkenyl-1,3-dicarbonyl compounds,[11] Antonioletti and coworkers demonstrated an efficient approach to 2,3,4,5-tetrasubstituted furans (Scheme 7).[12]

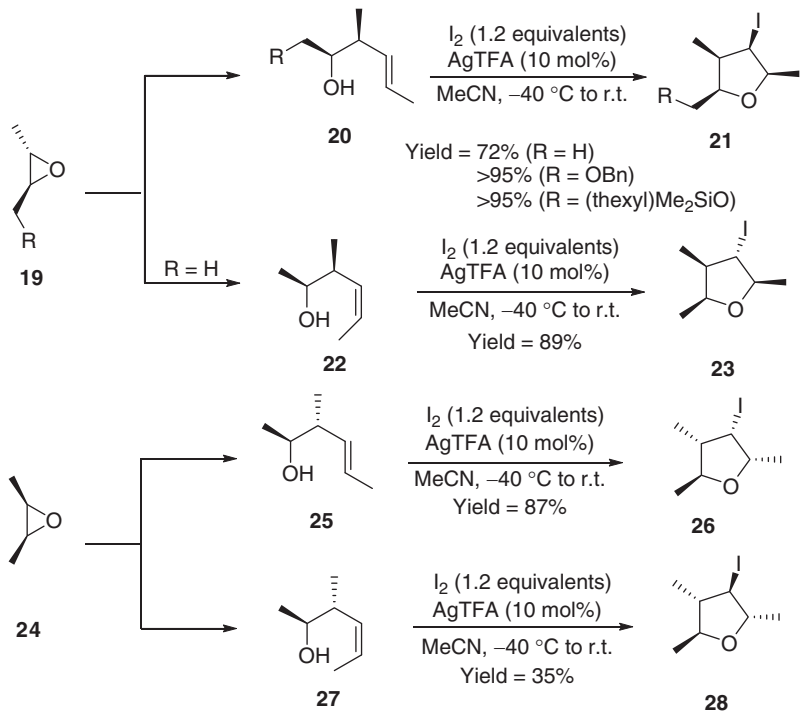
Iodine-mediated cyclizations of α-keto esters and ketones bearing allylic and homoallylic chains were investigated, which resulted in the formation of diverse functionalized five- and six-membered ring enol ethers (Scheme 8).[13] This methodology provides access to various functionalized cyclic ethers and tetrahydrobenzofuranones in moderate to very good yields.



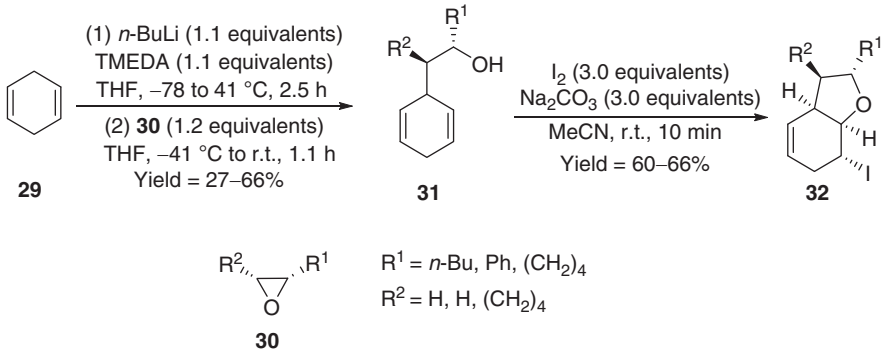
Scheme 3



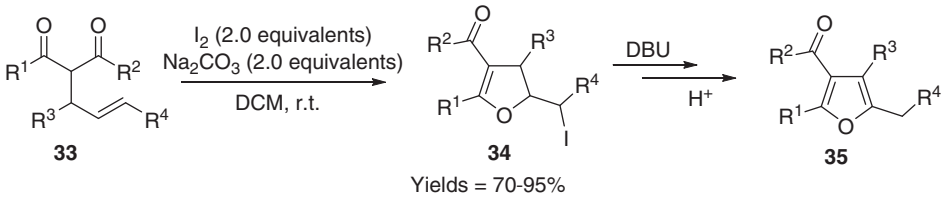
Scheme 4



Scheme 5



Scheme 6



Scheme 7

A simple and efficient strategy to generate highly polyfunctionalized compounds in a diastereoselective via a substrate-controlled halocyclization reaction is shown in Scheme 9.[14] IPy_2BF_4 was used for those iodofunctionalization reactions. A single diastereoisomer (single enantiomer) was favored when a phenyl or benzyloxy group was placed in a well-defined position of the terpene-derived compounds.

Mphahlele and coworkers developed a new methodology that combined electrophilic and oxidative properties associated with iodine to synthesize novel iodofunctionalized tetrahydrobenzofuranones and dihydrobenzofuran derivatives in a one-pot reaction (Scheme 10).[15]

To further demonstrate the versatility of this methodology, 3-phosphonylmethyl-2-(2-propenyl)-2-cyclohexenone derivative and its 5-methyl derivative were subjected to the same reaction conditions; the corresponding 2-iodomethyl-2,3-dihydrobenzofuran derivatives were formed (Scheme 11).[15]

Under the identical conditions (I_2, $NaHCO_3$, MeCN), Lee and Oh tested α-allyl-substituted β-keto sulfones and isolated the corresponding 4,5-dihydro-5-iodomethylfurans, which could be easily converted to furan derivatives with excess 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (DBU) (Scheme 12).[16]

Kang and coworkers developed a catalytic enantioselective iodoetherification to generate THFs with up to 90% *ee* using a chiral salen complex (Scheme 13).[17]

Hennecke and coworkers recently reported a promising organocatalytic approach to haloetherfications by desymmetrization of *in situ*-generated *meso*-halonium ions (Scheme 14).[18] By treatment of symmetrical diol with chiral phosphoric acid salt in the presence of electrophilic iodine source **73,** enantioenriched ether product **74** was obtained under the practical reaction conditions. The bromoetherification of **75** using NBS also gave good yield with *ee* up to 67%. Chiral phosphoric acid salt **72** could also promote the iodoetherification of **70** in an efficient way (56% *ee*).

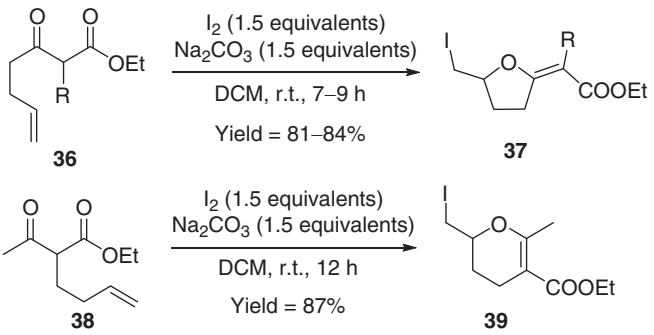
Knight and coworkers used iodine monobromide in the cyclization of dihydroxy ester to generate THFs exclusively in a 5-*endo* manner in a good yield with a diastereomeric ratio of 14:1 (Scheme 15).[19] The THF is the core structure of aplasmomycin precursor **79**.

Castillon also applied an iodoetherification strategy to form iodotetrahydrofuran in the natural products syntheses. The iodotetrahydrofuran as an equal mixture of diastereomers was obtained in a good yield as the key step in the synthesis of 1′-C-fluoromethyl- 2′,3′-dideoxycytidine **82** (Scheme 16).[20]

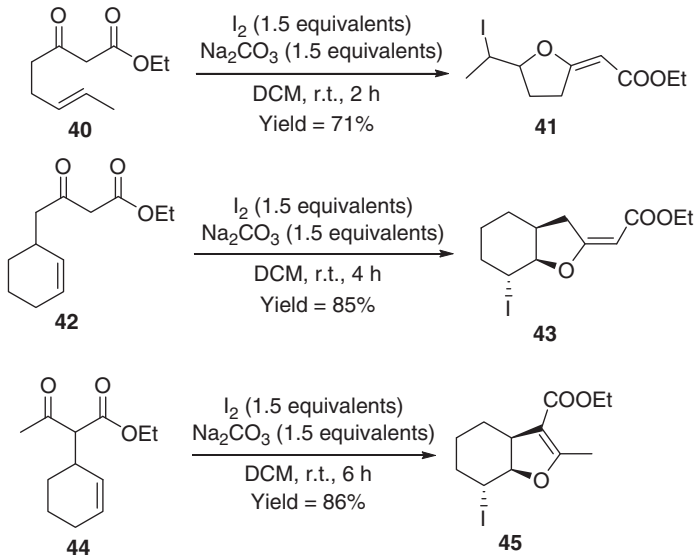
Another key structure is Peri and coworkers' synthesis of bicyclic sugar derivatives, which was further converted into $\alpha_v\beta_3$-selective arginine-glycine-aspartate (RGD) peptides; the synthesis was generated by iodocyclization (Scheme 17).[21] NIS induced a 5-*exo* cyclization with the adjacent benzyl ether oxygen in dry THF. Interestingly, a resolution of diastereomeric starting materials occurred; only the β-anomer cyclized formed a *cis*-fused ring, with the α-anomer recovered.

The iodocyclization is also suitable for more complex systems. Nicolaou and coworkers have extensively applied the iodocyclization reaction in total synthesis, for example in the construction of the ring of azaspiracid-1,2,3 (Scheme 18).[22] In the synthesis of fragment ABCD, **86** was exposed to NIS in the presence of $NaHCO_3$ to yield THF derivative **87** in 70% yield

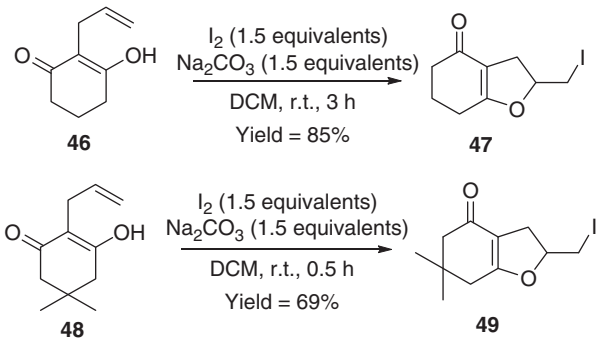
(a) Electrophilic Cyclization of β-Keto Esters Bearing a Monosubstitued Double Bond:



(b) Electrophilic Cyclization of β-Keto Esters Bearing Non-terminal C=C bonds



(c) Electrophilic Cyclization of Alkenyl-β-diketones:

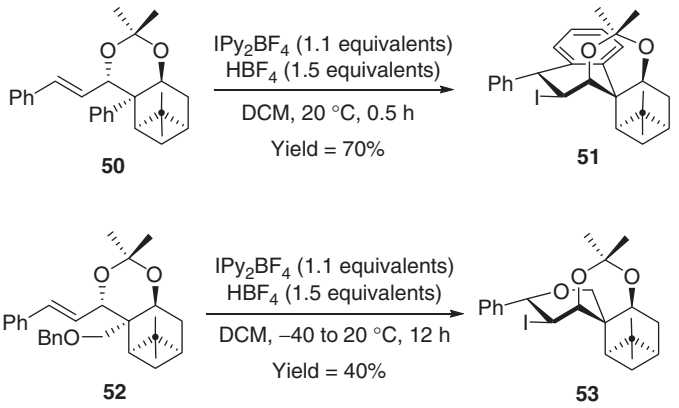


Scheme 8

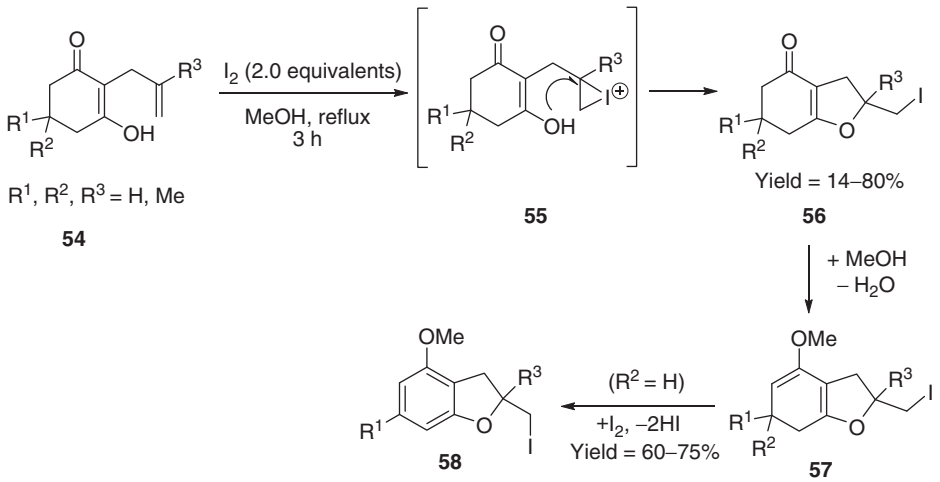
with the desired 2,5-*trans* stereochemistry. The same strategy has been used in constructing the ring G induced by NIS (Scheme 18).

In the total synthesis of (+)-lasonolide A, Kang et al. used iodine-induced substrate-controlled cyclization to afford a 27:1 mixture of *cis*-2,6-disubstituted tetrahydropyran and the corresponding *trans* isomer (Scheme 19).[23]

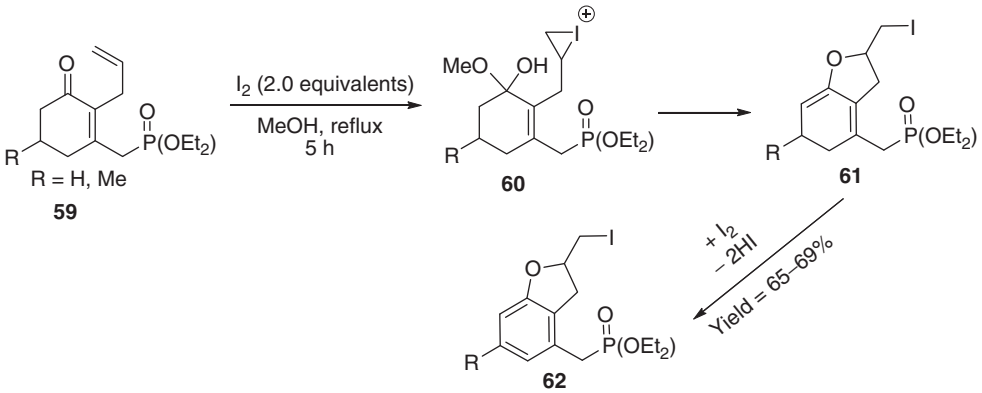
Some new chiral reagents have been developed to induce asymmetry together with electrophiles before racemizing, and the recent advances in this area have been highlighted.[24] Grossman and Trupp described the first reagent-controlled stereoselective halolactonization using a chiral dihydroquinidine–iodine complex. However, only a 15% *ee* in the 5-*exo* iodolactonization was achieved (Scheme 20).[25]



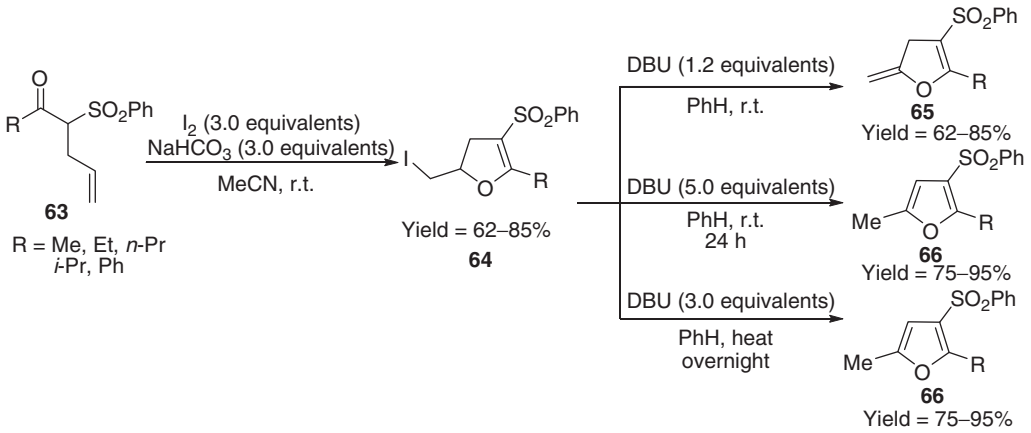
Scheme 9



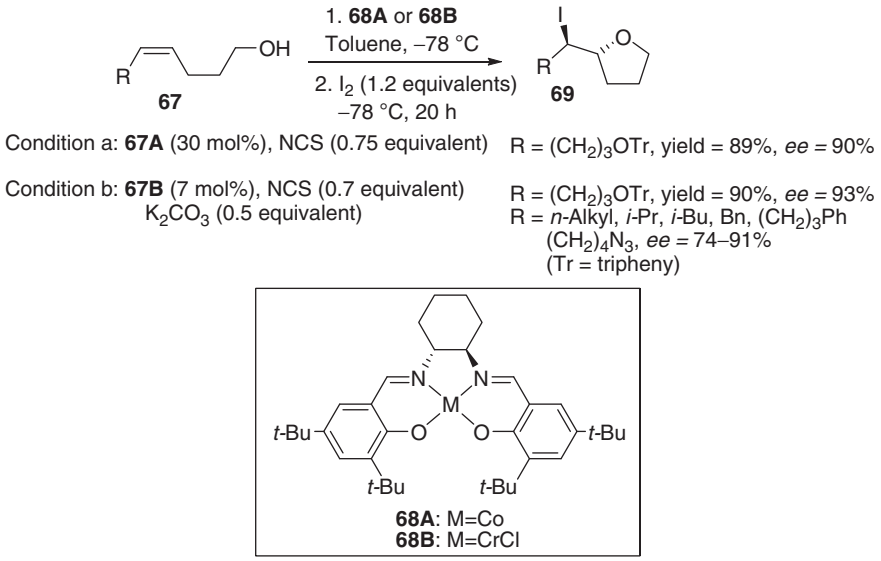
Scheme 10



Scheme 11



Scheme 12



Scheme 13

Rousseau and coworkers investigated the enantioselective 5-*endo* iodolactonization and found that ephedrine-derived halobis (amine) salt was the most effective one to give a 45% *ee* (Scheme 21).[26] But the chiral ammonium carboxylate gave only racemic product.

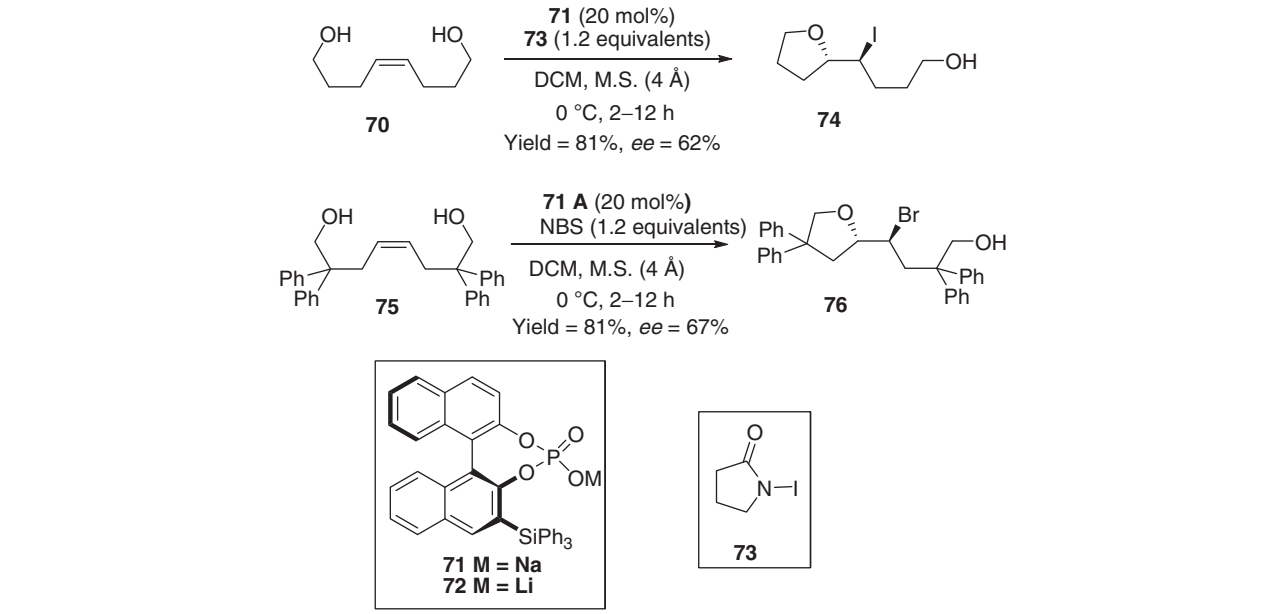
Taguchi and coworkers reported an example of enantioselective iodolactonization reaction induced by a titanium complex generated from (Me, Ph)-taddol and Ti(O*i*-Pr)$_4$. The corresponding (3*S*,5*S*)-3-allyl-3-hydroxy-5-(iodomethyl) dihydrofuran-2(3*H*)-one was obtained in a 65% *ee* (Scheme 22).[27]

Chiral cinchona alkaloid derivates induced low levels of asymmetry (<35% *ee*) during iodolactonizations of *trans*-5-aryl-4-pentenoic acids under the catalytic conditions (Scheme 23).[28] When stoichiometric amounts of alkaloids were used such as cinchonidine, exclusive six-member ring products were produced with a modest asymmetric induction.[29]

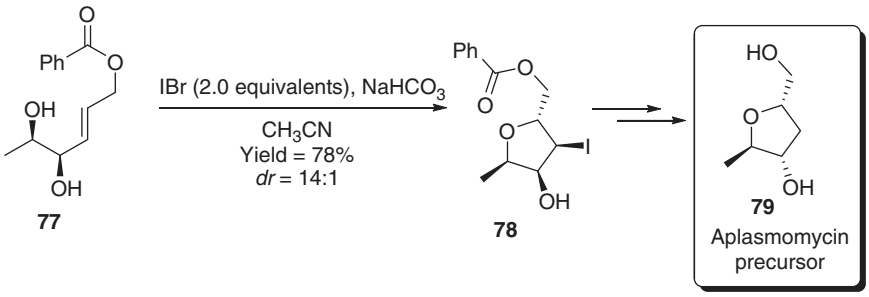
Jacobsen and coworkers used an anion-binding H-bonding catalysis strategy to accomplish enantioselective iodolactonization (Scheme 24).[30] In the case of 5-substituted hexenoic acid derivatives (such as **110**, and the transition states **116**, **117**, Scheme 24), a clear correlation between the electronic properties of the arene substituent and *ee* was observed, with electron-deficient derivatives undergoing more enantioselective cyclization. In the case of pentenoic acid **114**, a slightly low I_2 loading was needed for the optimal *ee*, and curiously, the absolute configuration was found to be opposite to the products of hexenoic acid cyclization.

Martin et al. discovered enantioselective iodolactonizations of diversely substituted olefinic carboxylic acids, which was promoted by a BINOL-derived bifunctional catalyst **120** (Scheme 25).[31]

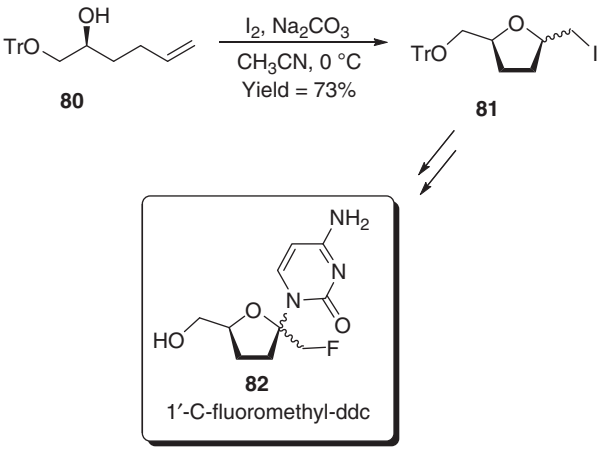
In Rizzacasa's synthesis of the phospholipase A2 inhibitor, cinatrin B, a lactone moiety was closed in a 5-*exo* iodolactonization of the suitably protected, arabinose-derived alkenyl acid **121**. This reaction proceeded in an efficient way in a high yield of the iodolactone **122** and a good diastereomeric ratio (94:6) (Scheme 26).[32]



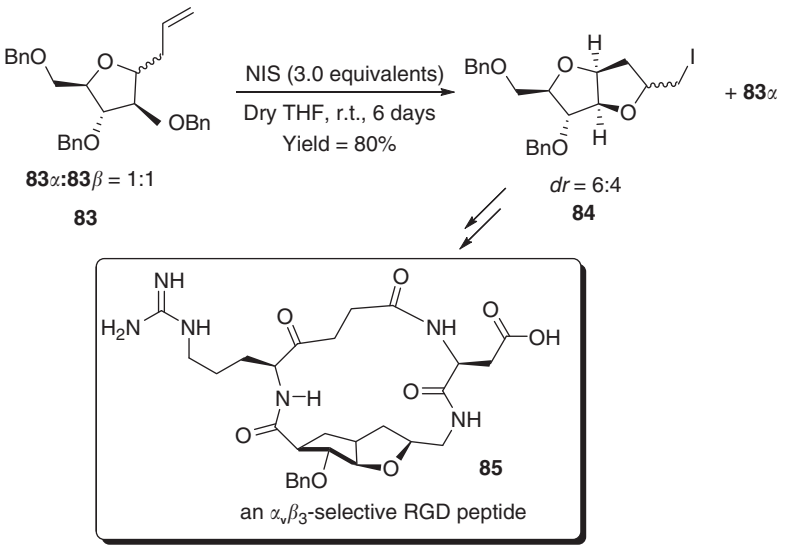
Scheme 14



Scheme 15



Scheme 16



Scheme 17

Hart and coworkers, in their synthesis of a *trans*-fused perhydroindan analog of hispidospermidin, performed a 5-*endo* iodolactonization of dihydrobenzoic acid (Scheme 27).[33]

In Kim's synthesis of pancratistatin, the stereochemistry of a hydroxy group was established by a 5-*exo* iodolactonization, elimination, and a subsequent hydrolysis/epimerization sequence (Scheme 28).[34]

Kishi and coworkers have used 6-*exo* iodolactonization of a chiral unsaturated acid to form the lactone with two new stereogenic centers ($dr > 20:1$) in their synthesis of fumonisin B2 (FB2). In contrasted with the sharpless asymmetric dihydroxylation of the 2-alkenes, it was considered as a better option (Scheme 29).[35]

In the synthesis of epoxyquinals A and B by Hayashi and coworkers, an iodolactonization of an *in situ*-generated bicyclic ether acid salt was performed. Then under basic conditions, iodolactone was opened with subsequent epoxide formation and methylation, which cleaved the ether, resulting in the formation of substituted cyclohexenol by treatment with lithium diisopropylamide (Scheme 30).[36]

Clarke et al. notified a significant solvent effect when iodonium acetate was used in the synthesis of the DEF ring of hexacyclinic acid. Taking $CHCl_3$ as solvent, a chair–chair conformation was proposed to form the bicyclic lactone **140** as the only product. Alternatively, using HOAc as solvent, a boat–boat transition state led to the formation of the desired product **141** (Scheme 31).[37]

In the synthesis of both FB2 and (–)-cinatrin B, iodolactonization was used to afford high diastereoselectivity (Scheme 32).[32,35]

Jung and coworkers synthesized 6-epiplakortolide E, a potent anticancer target, by using an iodolactonization of a cyclic peroxide in the presence of I_2 and $NaHCO_3$ with a long reaction time at room temperature (Scheme 33).[38]

Silver(I) triflate could accelerate iodocyclization of carbamates bearing electron-deficient olefins to give α-iodoesters in excellent *anti*-ring stereoselectivity. Epimerization happened during this process, and the rate of epimerization is solvent dependent (Scheme 34).[39]

Minakata and coworkers developed a cyclizative atmospheric CO_2 fixation methodology by allyl amines, which is an efficient, metal/base-free process (Scheme 35).[40] *t*-BuOI played an important role in the transformation to cyclic carbamates. The method was applicable to a wide range of unsaturated amines under mild conditions with good yield.

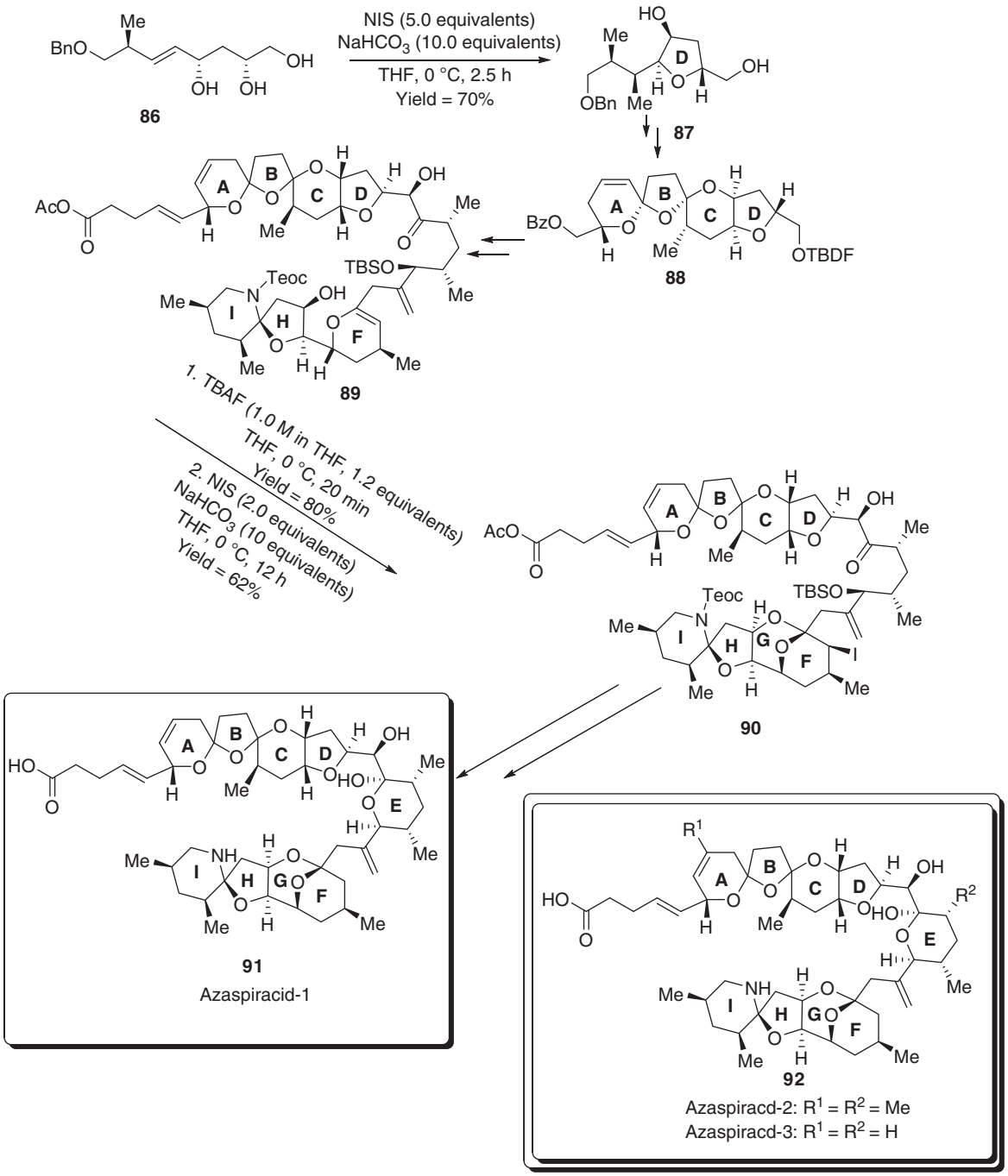
The homoallylic *tert*-butyl carbonate was treated with iodine in MeCN at –20 °C to generate the iodocarbonate in a high diastereoselectivity ($de = 95\%$) favored *syn*-isomer, which could be separated by column chromatography (Scheme 36).[41]

Besides the hydroxyls, esters and ketones, imides could also realize *O*-halocyclization. Generally, *O*-cyclization is preferred to *N*-cyclization in the halocyclization reactions of alkenylated amide, carbamate, and urea derivatives, which could be explained by Hard and Soft Acids and Bases theory shown in Figure 2.[42] Of course, both the *O*-cyclization and *N*-cyclization are controllable depending on the experimental conditions.[2e] Some *O*-cyclization examples of imides are summarized in the following section.

When β,γ-unsaturated amides were subjected to *t*-BuOCl and I_2 in dichloromethane (DCM), unsaturated iminolactones were obtained, which are hydrolyzed to the corresponding butenolides by the treatment with 3 N HCl (Scheme 37).[43]

I_2-promoted cyclization of multisubstituted dienamides with halogenated cyclic iminoethersin excellent yields with perfect selectivity was reported by Xi et al. (Scheme 38).[44] *O*-attack *exo*-cyclic imino ethers are the only product and no *N*-attack products or *O*-attack *endo* products are formed.

Some more examples for diastereomeric preferences in the halolactonization of amides are shown in Scheme 39.[2e,2f]



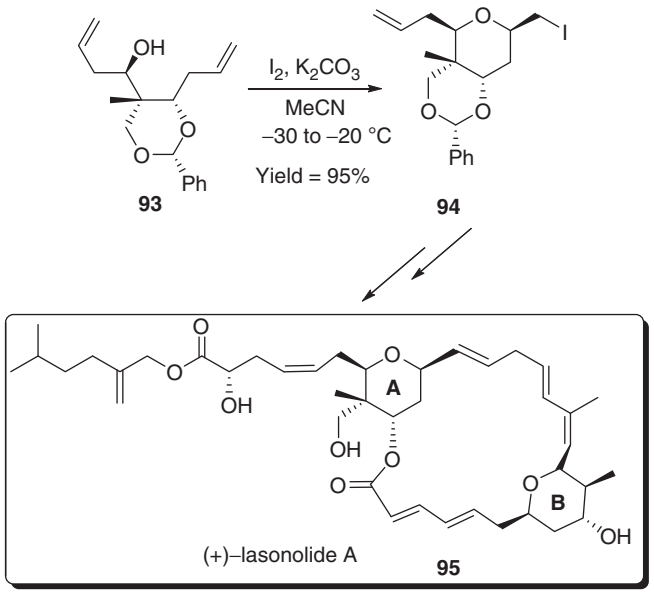
Scheme 18

Intramolecular electrophilic cyclization of quinolones with iodine afforded racemic *cis*-diastereoisomers (Scheme 40).[45] The results showed that the stereochemistry was influenced by the preexisting chirality of the alkenyl side chain. The transition state was proposed in Scheme 40. The 4-hydroxy group adopted an equatorial position and the C=O bond coordinates to the activated alkene via oxygen leading to form *cis*-diastereoisomer predominantly.

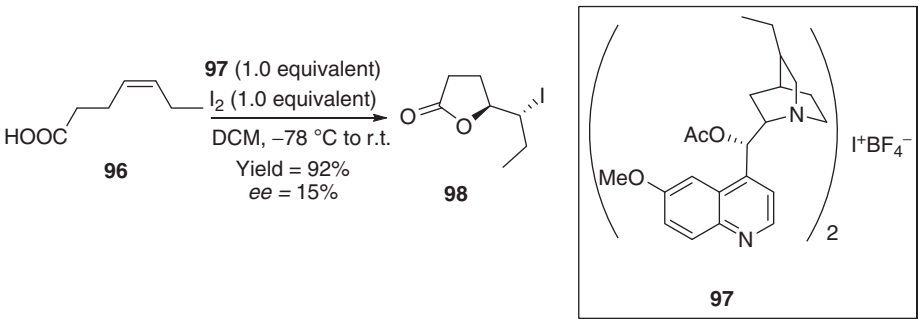
An iodolactonization of unsaturated chiral amide was applied in the synthesis of (+)-citreoviral by Kobayashi and coworkers. The reaction could proceed smoothly to afford iodolactone in a 92% yield as a single isomer (Scheme 41).[46]

An example of the preparation of 2,5-disubstituted THFs from isoxazoline-based substrate is shown in Scheme 42.[47]

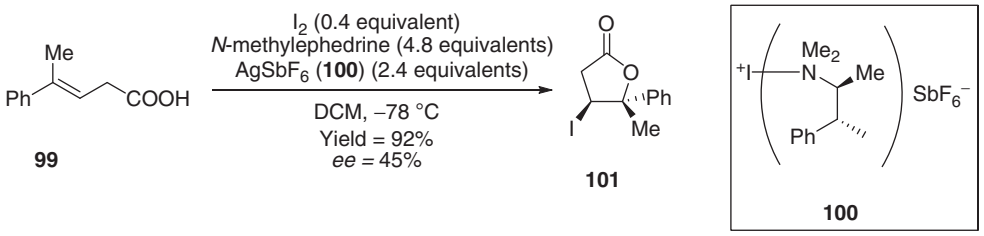
Dioxanes, trioxanes, or trioxepanes could be obtained from unsaturated hydroperoxyacetals and hydroperoxyketals via electrophilic cyclization in the presence of I_2 and base (Scheme 43).[48] Different conditions were screened; two isomers could be obtained from all of these reactions in different ratio.



Scheme 19



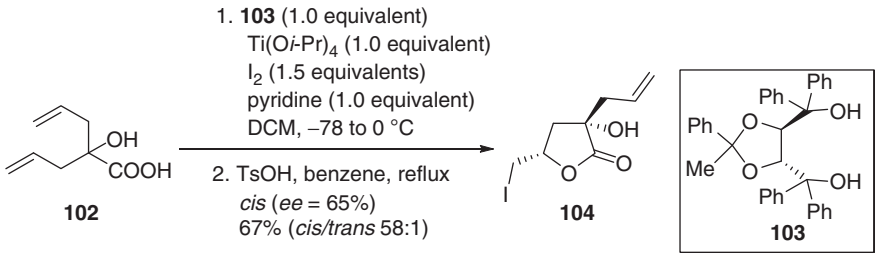
Scheme 20



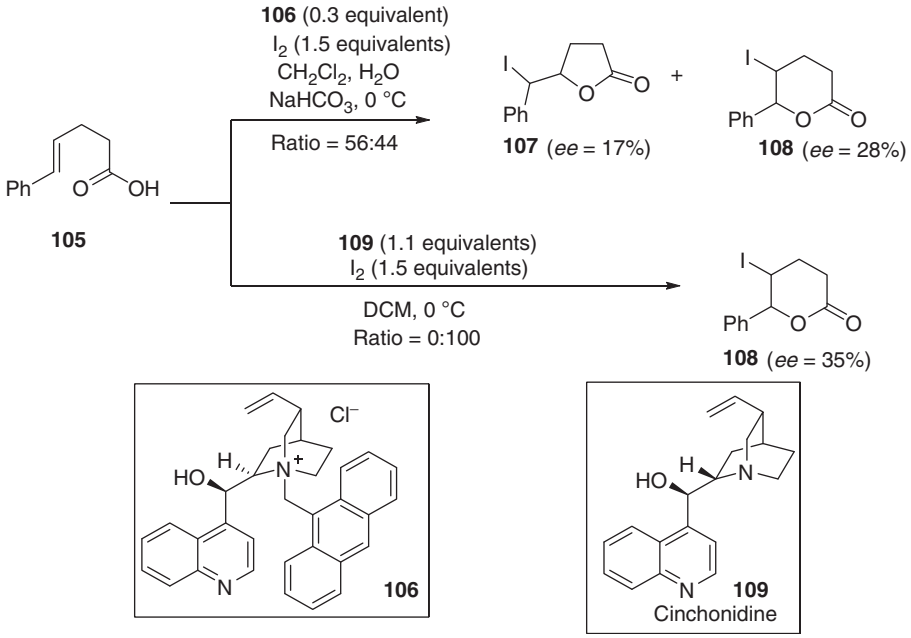
Scheme 21

Rodriguez and coworkers reported one example of an epoxide serving as the nucleophile in an iodoetherification reaction.[49] Two diiodo ethers were isolated and characterized. If iodonium ion formation from the top face as **198a**, 6-*endo* cyclization product **199** was obtained, otherwise it led to the formation of the THF **200** via a 5-*exo* cyclization from the bottom face via intermediate **198b** (Scheme 44).

An example of using sulfoxides as nucleophiles was reported by Abe and Harayama.[50] Compound **201** underwent a 5-*exo* cyclization to provide the tricyclic intermediate **202**, which was further hydrolyzed to afford the inverted sulfoxide **204**, competing with the Pummerer rearrangement to form 1,3-oxathianes **203** (Scheme 45).



Scheme 22



Scheme 23

4.07.2.1.1.2 Cyclization involving alkynes

Compared to alkene cyclizations, the major difference of alkyne is that the electrophilic group in the initial product may be a vinyl substituent, such as vinyl iodide, which is the most useful precursors for cross couplings.

Liang and coworkers reported an example of electrophilic cyclization with 1,4-butyne-diols derivates, which resulted in highly substituted dihalogenated dihydrofurans and dihydro-2*H*-pyrans in moderate to excellent yields (Scheme 46).[51]

Zhou and coworkers developed a facile and efficient method for the synthesis of 2,4-dihalo-3-thio-furans from 4-thiobut-2-yn-1-ols (Scheme 47).[52] A proposed mechanism including 1,2-migration of the thio group is shown in Scheme 48. The iodonium ion **213** was generated via iodine ion attacking the triple bond, followed by an intramolecular nucleophilic attack of sulfur atom offering thiiranium **214**. In the presence of base, intermediate **214** could produce thiiranium zwitterion intermediate **215,** which could form intermediate **216** through the intramolecular nucleophilic attack. The product **212** could be obtained via elimination and dihalogenation.

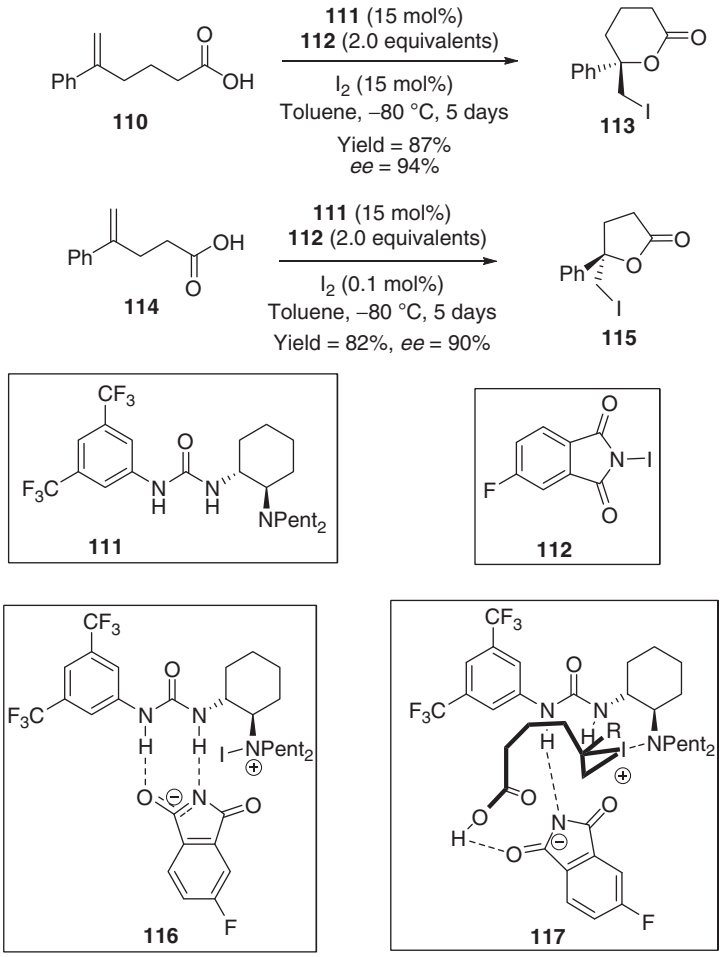
Knight and coworkers have systematically investigated the cyclization of 3-alkynyl-1,2-diol derivates with iodine and $NaHCO_3$ mixture in MeCN (Scheme 49).[53] Aromatization via the elimination of **218** provides an efficient way to synthesize *β*-iodofurans.

The iodocyclization of 2-enynols affords fully substituted 5-ylidene-2,5-dihydrofurans with high regio- and stereoselectivity under mild reaction conditions. This methodology provides a highly efficient route to access oxygen heterocycles bearing an *exo*-cyclic carbon–carbon double bond (Scheme 50).[54]

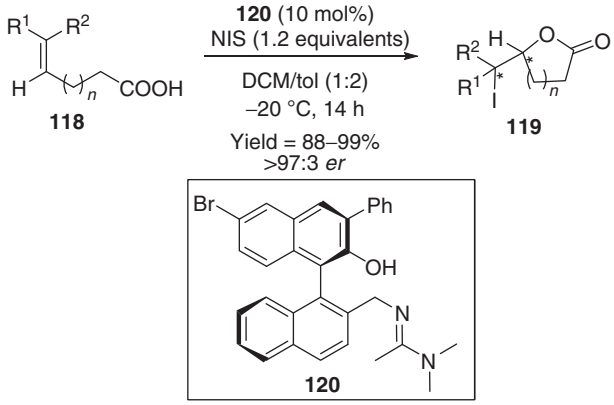
2-Substituted 3-iodobenzo[*b*]furans could be prepared by the iodocyclization of 2-alkynylanisole derivatives (Scheme 51).[55] This type of product is a useful synthetic intermediate to introduce different groups to the 3-position via cross-coupling reactions.

Both I_2/CAN in MeCN and I_2 in DCM could induce cyclization of **225** to afford 3-iodochromenones (3-iodo-4*H*-1-benzopyran-4-ones) **226** in good yields (Scheme 52).[55,56]

A useful strategy to construct 2,3-disubstituted furopyridines induced by iodine at room temperature is developed by Arcadi and coworkers (Scheme 53).[57]

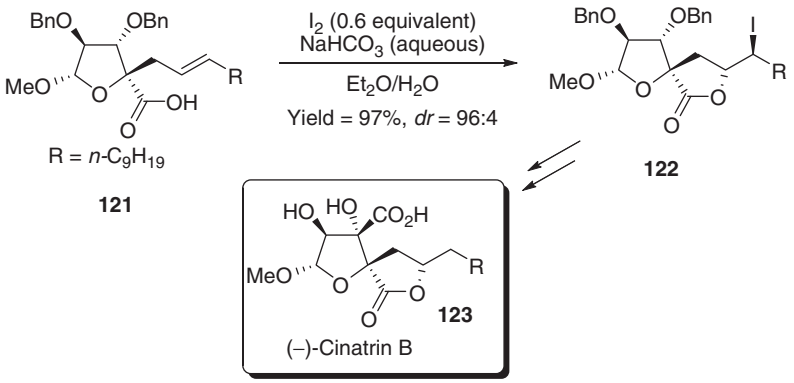


Scheme 24

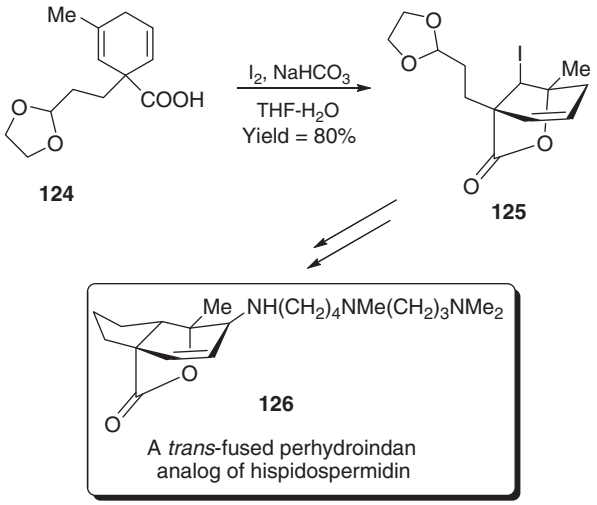


Scheme 25

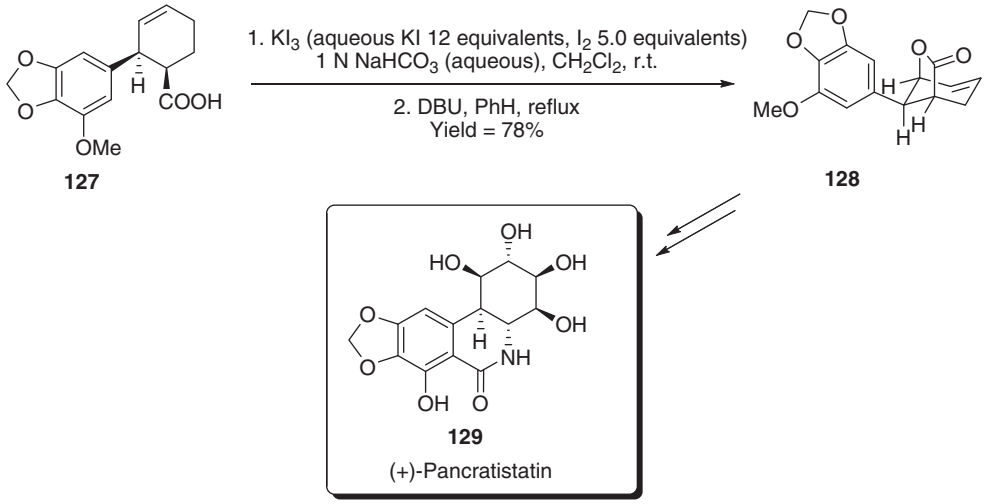
Two protocols for the synthesis of 4-iodo-3-furanones from 2-alkynyl-2-silyloxy carbonyl compounds have been developed (Scheme 54).[58] A plausible mechanism is described in Scheme 54, which includes a heterocyclization with a 1,2-alkyl shift. As shown in path A, after the formation of iodonium intermediate **231** via the coordination of iodine to the triple bond, oxonium ion **232** could be formed by nucleophilic attack of the carbonyl oxygen. Subsequent 1,2-shift gives 4-iodo-3-furanone **230**. In the presence of Au (Path B), it proceeds through the coordination of Au cation to the alkynyl **233** followed by 1,2-migration of the resulting oxonium ion **234** to yield **235**. Then a rapid iododemetalation occurs in the presence of external NIS leaded to 3-furanone **230** containing the iodo substituent at C4.



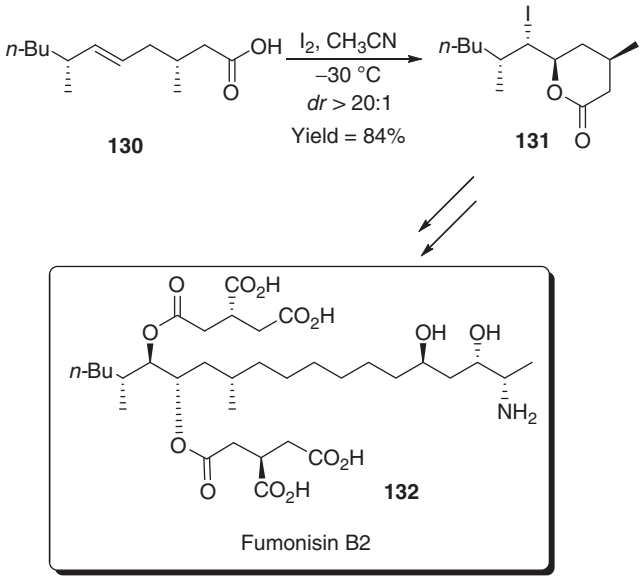
Scheme 26



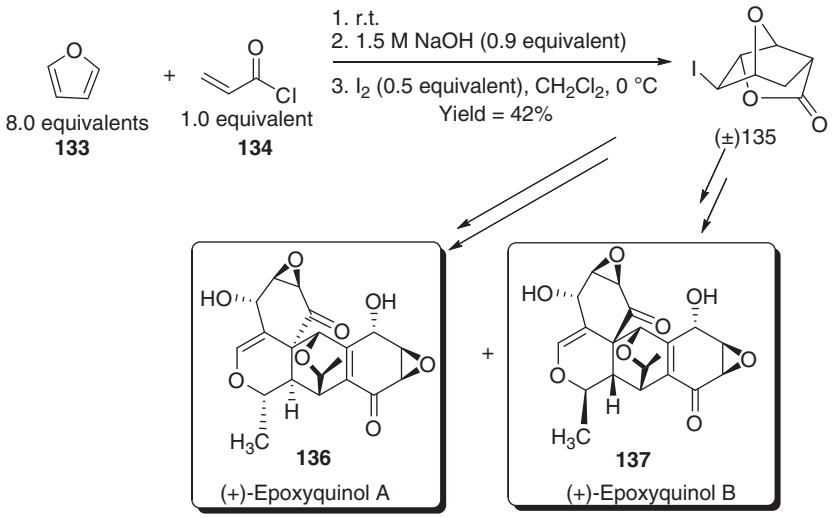
Scheme 27



Scheme 28



Scheme 29



Scheme 30

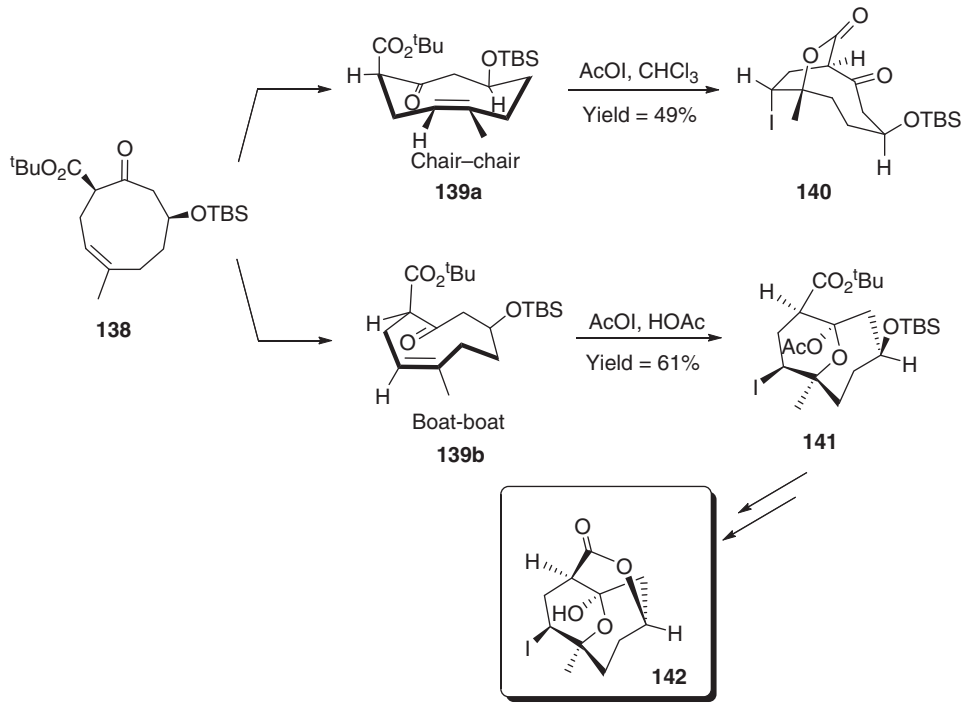
Huang and coworkers report the electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones to afford highly substituted furans in good to excellent yields under mild conditions (Scheme 55).[59]

Efficient syntheses of substituted oxygen-containing heterocycles and carbocycles have been developed by Larock's group, using acetylene-containing aldehydes and ketones as substrates (Scheme 56).[60] During their further efforts, Larock and coworkers have realized, for the first time, the iodine-catalyzed selective synthesis of iodo-pyrano[4,3-*b*]-quinolines and *ortho*-alkynyl esters from *ortho*-alkynyl aldehydes (Scheme 57).[61] This novel oxidative esterification process provides a powerful tool to construct a wide range of functionalized pyranoquinolinones as well as isocoumarin.

The cyclofunctionalization of 2-(1-alkynyl)-2-alken-1-ones generated highly substituted halofurans in good to excellent yields under extremely mild conditions using the I_2/K_3PO_4 system (Scheme 58).[62]

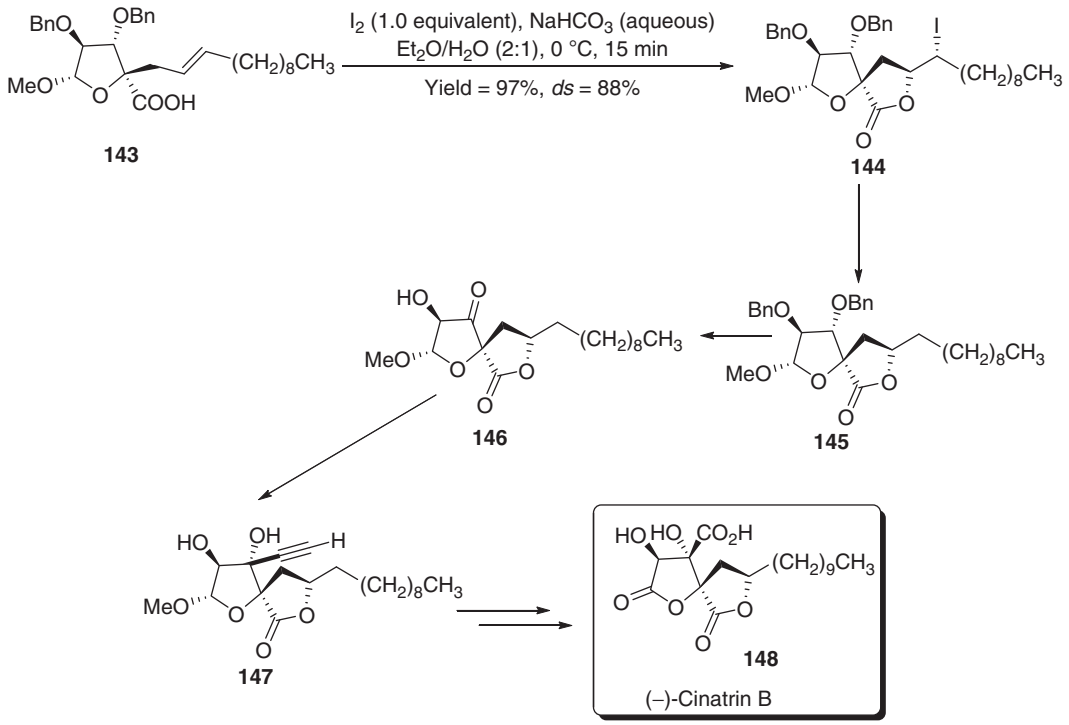
I_2-Mediated electrophilic cyclization of α,α-disubstituted β-alkynyl esters could afford the functionalized γ-lactone in an excellent yield (Scheme 59).[63]

Liang and coworkers developed an iodocyclization approach of propargylic epoxides to form polysubstituted 3-iodofuran (Scheme 60).[64] After the formation of iodonium intermediate **253,** subsequent *anti* attack by the oxygen on the iodonium ion and elimination of a hydrogen cation generated 3-iodofuran **252**.

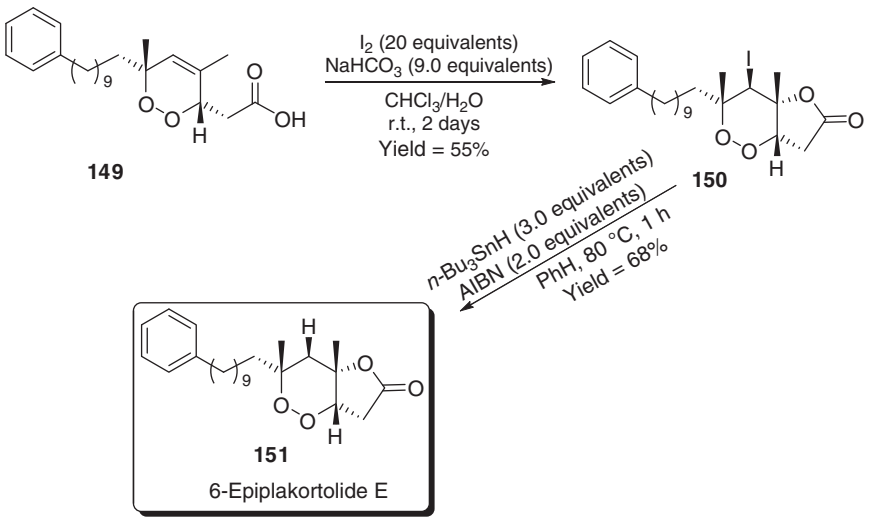


A model DEF-ring system of hexacyclinic acid

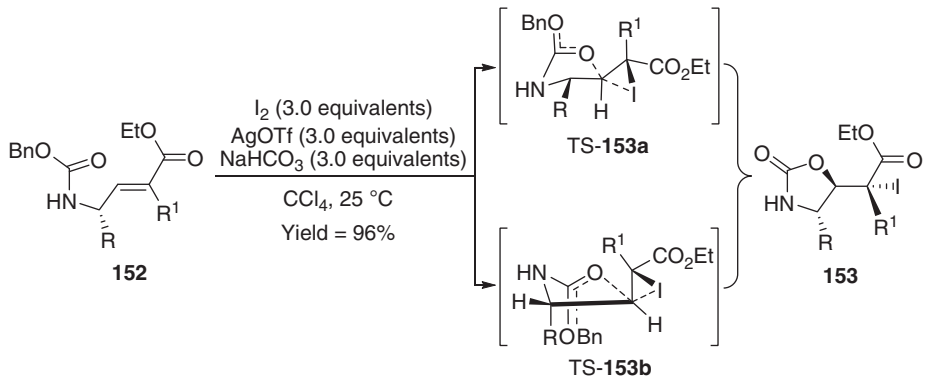
Scheme 31



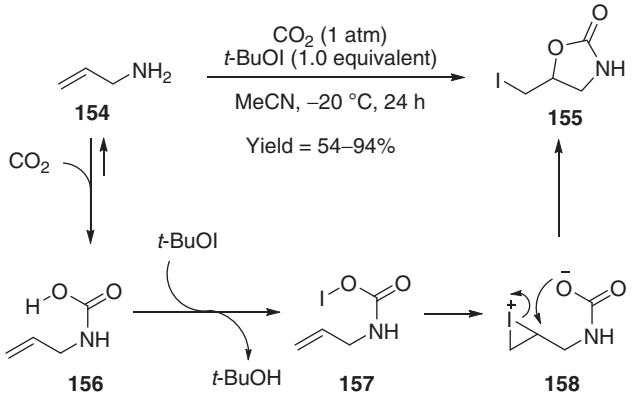
Scheme 32



Scheme 33

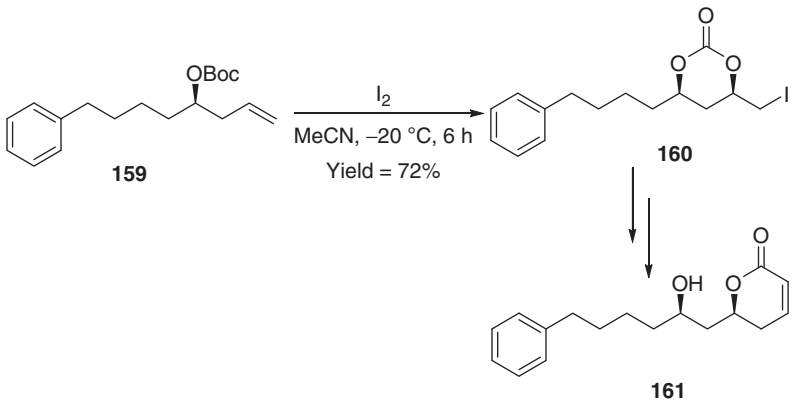


Scheme 34



Scheme 35

Substituted 2-alkyn-1-one *O*-methyl oximes could be cyclized in the presence of ICl to give the corresponding 3,4,5-trisubstituted isoxazoles in high yields under mild reaction conditions (Scheme 61).[65] This process can be readily scaled up on multigram scale.



Scheme 36

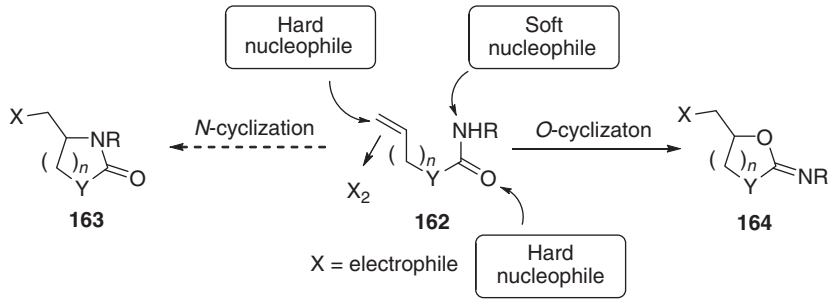
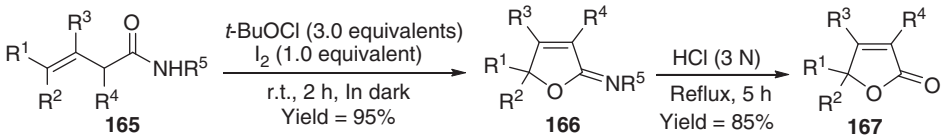
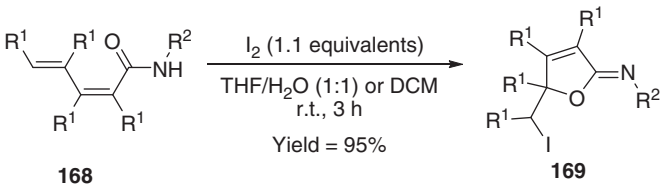


Figure 2 Cyclization of amides.



Scheme 37

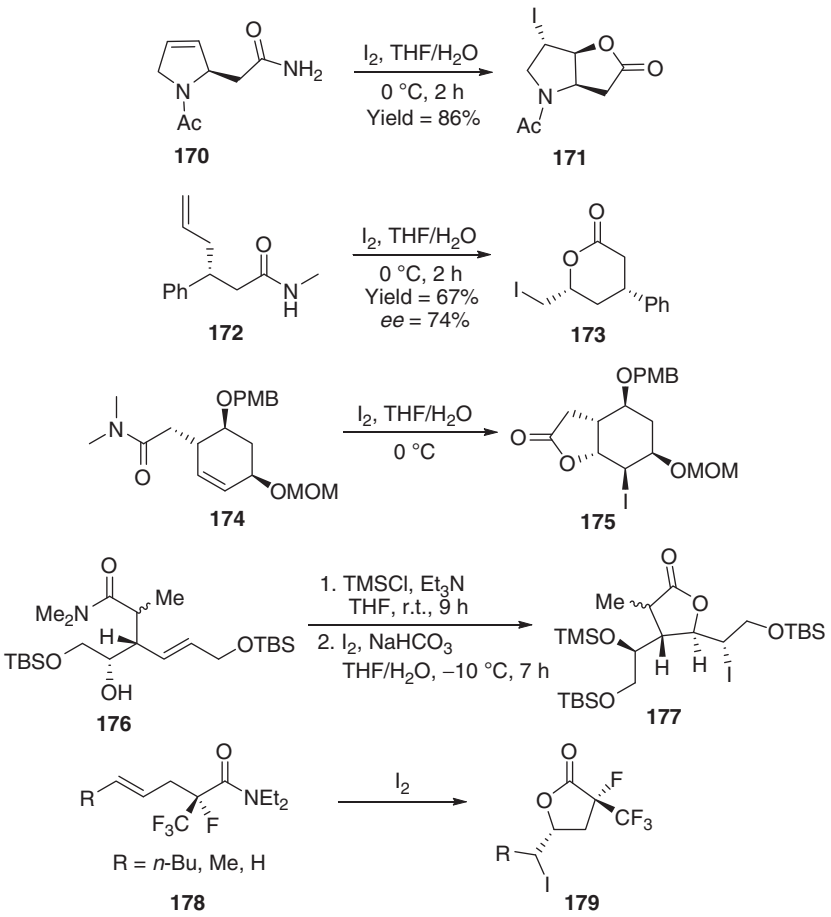


Scheme 38

5-*Endo-dig* electrophilic cyclization of 5-alkynyl-2′-deoxyuridines with NIS or *N*-bromosuccinimide in acetone at room temperature gives 3-(2′-deoxy-*β*-D-ribofuranosyl)-5-halo-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-ones that usually precipitate from the reaction mixture (Scheme 62).[66]

4.07.2.1.1.3 Cyclization of allenes

The history of allenes dates back to 1874, when Jacobus H. van't Hoff predicted the correct structure of this type of compounds. Till today, lots of natural products and pharmaceuticals containing the allene moiety are discovered, and some reactions with allenes have been successfully applied for the efficient synthesis of natural products.[67] The rich abundance of electrophilic reactions of alkenes and alkynes indicates that allenes should also undergo electrophilic reactions easily.[68]



Scheme 39

Ma et al. have explored a large number of reactions of allenes with many different electrophiles.[69] In the presence of I_2, 3-allenoic acids could be cyclized to afford *β*-halobutenolides (Scheme 63).[70] With 4,5-allenoic acids, the iodolactonization reaction in cyclohexane with I_2 or NIS afforded the five-membered lactones exclusively in fairly good yields and a very high *Z*/*E* selectivity (Scheme 64).[71]

Besides the allenoic acids, allenoates are successfully applied in iodolactonization. A direct iodolactonization of 2,3-allenoates with I_2 was successfully developed in MeCN and H_2O, affording *β*-iodobutenolides in good to excellent yields (Scheme 65).[72]

Ma and coworkers developed a facile and efficient method for the synthesis of 4,5-dihydrofuran derivates via electrophilic cyclization of 2-(2′,3′-allenyl)acetylacetates in the presence of I_2 at room temperature (Scheme 66).[73]

To extend the application of iodolactonization of allene, Ma et al. applied this methodology in the synthesis of (+)-*trans*-whisky lactone **270a** in 11 steps from propargyl alcohol recently (Scheme 67).[74a] By using a new electrophilic iodination reagent, the same group reported a highly stereoselective iodolactonization of 4-allenoic acids, which has been successfully utilized in the synthesis of naturally occurring compounds (+)-*cis*-whisky lactone **270b**.[74b]

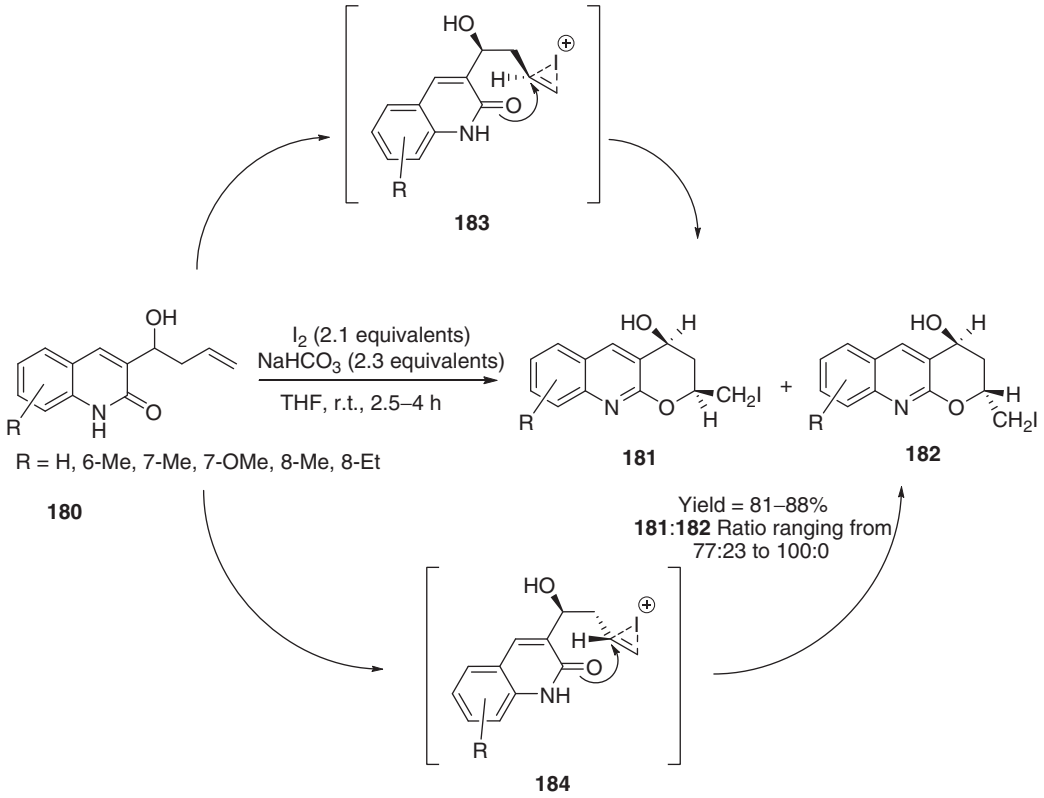
4.07.2.1.2 N-nucleophiles

4.07.2.1.2.1 Cyclization involving alkenes

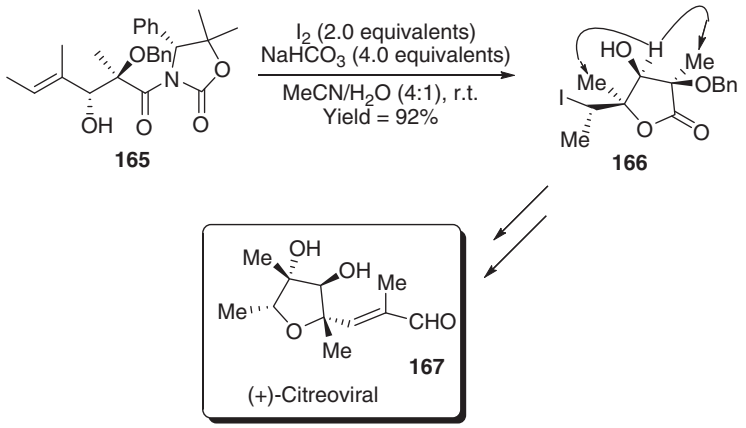
A simple and efficient method for the cyclization of various alkenylamides using chloramine-T and I_2 was developed by Minakata's group (Scheme 68).[75]

Gouverneur et al. reported the first examples of iodocyclization with functionalized allylic fluorides bearing nitrogen nucleophiles. It is an efficient method to prepare 3-fluoropyrrolidines via 5-*exo*-*trig* cyclization in high yields and with good diastereocontrol (Scheme 69).[76]

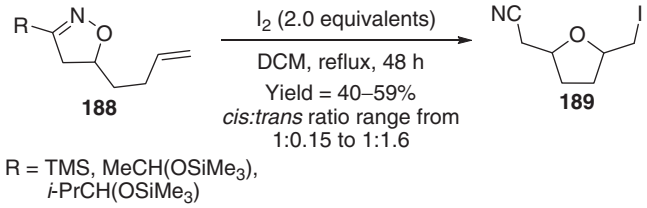
Huang et al. have developed a highly stereoselective iodocyclization reactions of methylenecyclopropanes with iodine in the presence of K_2CO_3, leading to the formation of 1-iodo-2-aryl-3-azabicyclo[3.1.0]hexanes in good yields under mild conditions (Scheme 70).[77] Methylenecyclopropanes are highly strained but readily accessible molecules, and the relief of ring strain provides a potent thermodynamic driving force, which makes it a useful synthetic intermediate.



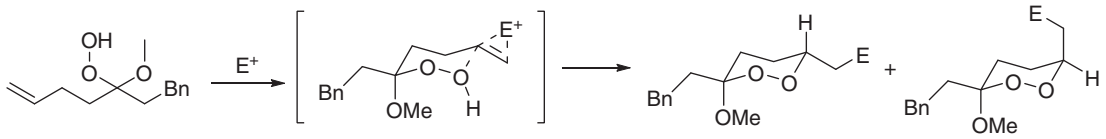
Scheme 40



Scheme 41

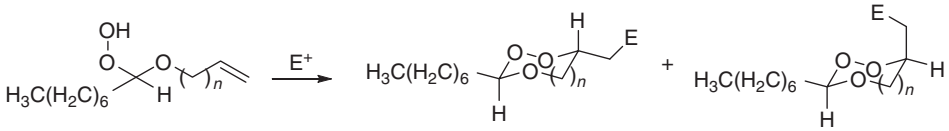


Scheme 42



190 **191** **192** **193**

Reagent	E	Temperature (°C)	Solvent	Yield (%)	**192:193**
Pyridine/I_2	I	0	DCM	50	1:1
t-BuOK/I_2	I	r.t.	THF	48	1:1.7
t-BuOK/I_2/18-C-6	I	r.t.	Benzene	34	1:2.5



194 **195** **196**

Reagent	E	Temperature (°C)	Solvent	Yield (%)	**195:196**
n-BuLi/I_2	I	–78	THF	20	10:1
KH/I_2	I	0–r.t.	THF	24	7:1
t-BuOK/I_2/18-C-6	I	r.t.	Benzene	22	6:1
t-BuOK/I_2	I	0	DCM	19	4:1
Cs_2CO_3/I_2	I	r.t.	THF	12	10:1

Scheme 43

4.07.2.1.2.2 Cyclization involving alkynes

The electrophilic cyclization of propargylic aziridines is developed to construct 3-iodopyrroles with a variety of substituents (Scheme 71).[78]

Kundu and coworkers have developed an efficient synthetic strategy toward the synthesis of the naturally occurring indoloazepinone scaffold via a three-component reaction involving indole-2-carboxamide, 1,3-disubstituted propargyl alcohols, and I_2 via a regioselective 7-*endo-dig* iodo-cyclization pathway (Scheme 72).[79]

The Larock group developed a method for the synthesis of a wide variety of *N*-alkyl-3-iodoindoles under very mild reaction conditions by the Pd/Cu-catalyzed cross coupling of *N*,*N*-dialkyl-*o*-iodoanilines and terminal alkynes, followed by electrophilic cyclization with I_2. Alkyl-, aryl-, and vinylic-substituted alkynes all underwent iodocyclization in excellent yields (Scheme 73).[80]

By using substrate **286** bearing a hydroxyl on the benzyl position, Flynn et al. described a highly selective *endo*/*exo* iodocyclization procedure for a divergent synthesis of indoles, quinolines, and quinolinones (Scheme 74).[81]

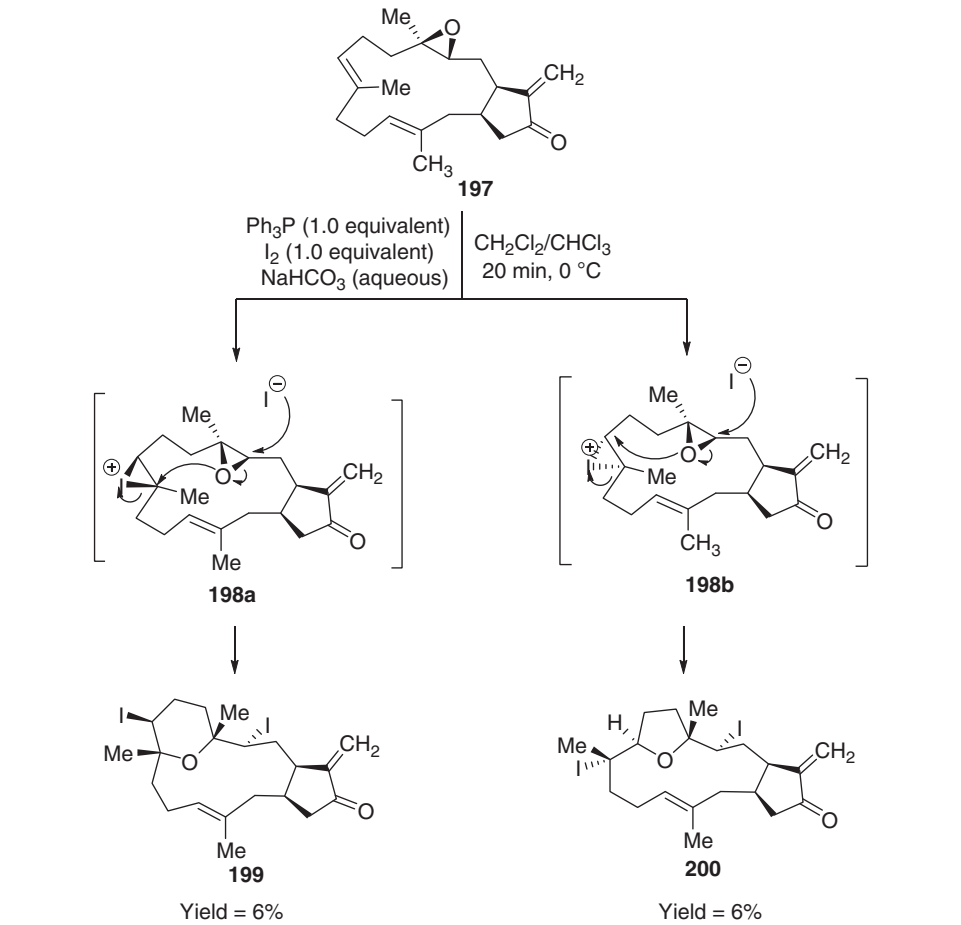
Changing the protecting group of nitrogen from dimethyl to Ts, Liang et al. reported an efficient and highly regioselective protocol for preparing 3-iodoquinolines (Scheme 75).[82] The resulting 3-iodoquinolines can be further functionalized by using cross-coupling reactions.

When the terminal alkynes were used as substrates, Chan et al. developed an NIS-mediated cycloisomerization reaction of 1-(2′-anilinyl)prop-2-yn-1-ol to gem-3-(diiodomethyl)indolin-2-one and 2-(iodomethylene)indolin-3-one. The reaction was shown to be chemoselective that secondary and tertiary alcoholic substrates exclusively produced the 3- and 2-oxindole products, respectively (Scheme 76).[83]

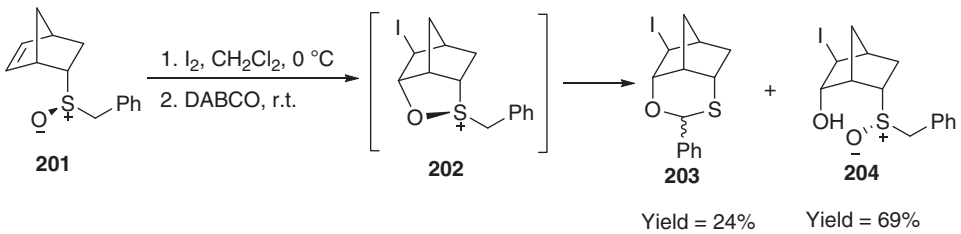
Tellitu and coworkers report an example of the hypervalent iodine reagent PIFA-promoted intramolecular electrophilic cyclization of alkynyl amides and alkynyl carboxylic acids, leading to the formation of pyrrolidinone and lactone skeletons, respectively, in a very efficient way (Scheme 77).[84]

Electrophilic cyclizations of α,β-alkynic hydrazones by molecular iodine afford synthesis of 4-iodopyrazoles in good to high yields (Scheme 78).[85]

Wu and coworkers have described a highly efficient electrophilic cyclization of N′-(2-alkynylbenzylidene)-hydrazide with I_2, Br_2, or ICl in DCM at room temperature. It provides an efficient method to construct functionalized isoquinolinium-2-yl amides (Scheme 79).[86] Recently, they reported a multicomponent reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, electrophile (bromine or iodine), and ketone or aldehyde under mild conditions, which generates the halo-containing *H*-pyrazolo[5,1-α]isoquinolines in good yields (Scheme 80).[87]



Scheme 44



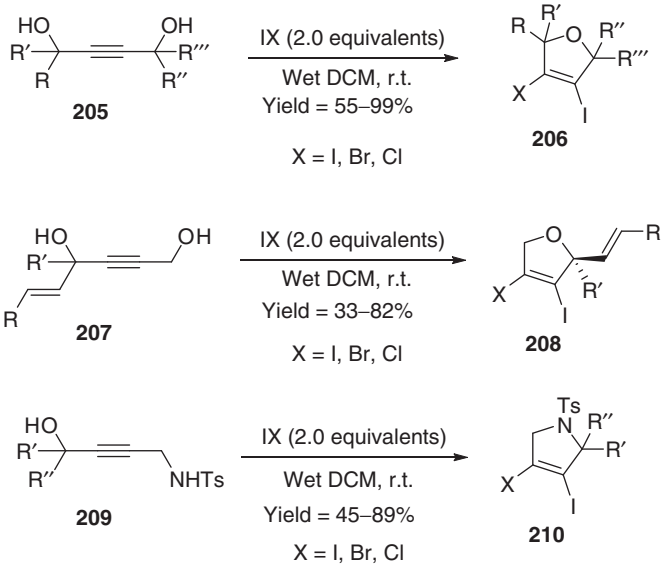
Scheme 45

Verma et al. demonstrated an I_2-induced electrophilic cyclization, which is a facile synthesis of substituted pyrrolo[1,2-a]quinolines (Scheme 81).[88]

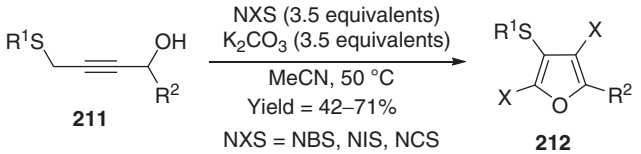
Li et al. have developed an electrophilic tandem cyclization protocol for the synthesis of haloisoquinoline-fused benzimidazoles via CuI-promoted tandem cyclization of 2-ethynylbenzaldehydes with *o*-benzenediamines and iodine (Scheme 82).[89] This protocol allows the formation of imidazo[1,2-*a*]pyridine ring in a one-pot reaction through the electrophilic annulation.

In 2007, Yamamoto and coworkers presented a general and flexible approach to synthesize highly substituted isoquinoline building blocks, which can be further functionalized (Scheme 83).[90] Depending on the nature of the substrates employed, acidic, basic, or neutral reaction conditions can be used, which makes this method compatible with sensitive, highly functionalized molecules. Their further research was reported in 2008, which presented a general and flexible approach to access highly substituted isoquinoline building blocks (Scheme 84).[91] They finished the total synthesis of norchelerythrine by using the developed methodology to construct ring B (Scheme 85).

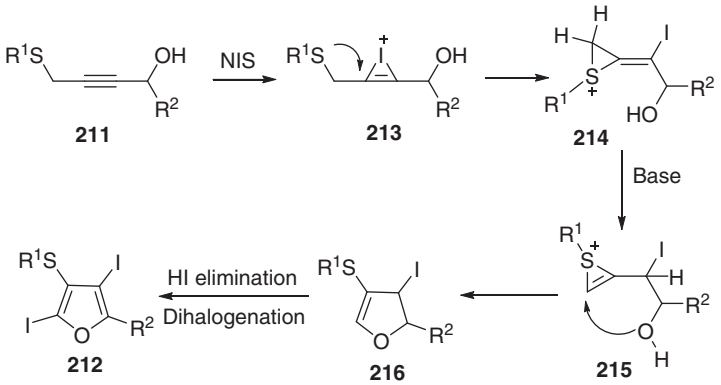
Yamamoto et al. and Wu et al. separately reported an efficient procedure for the synthesis of 3,4-disubstituted iodoisoquinoline *N*-oxides from 2-alkynylbenzaldoximes (Scheme 86).[92]



Scheme 46



Scheme 47



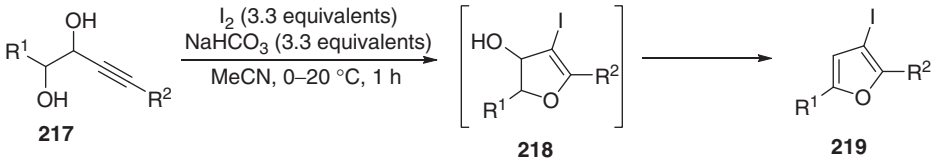
Scheme 48

4.07.2.1.3 C-nucleophiles

4.07.2.1.3.1 Cyclization involving alkenes

Taguchi and coworkers reported some iodocarbocyclization examples induced by chiral titanium taddolate **322**.[93,94] When CuO and the chiral titanium taddolate **322** were used for the iodocarbocyclization of dibenzyl 2-(4-pentenyl)malonate, it gave the corresponding product **323** in a 96% yield with a 85% *ee* (Scheme 87).[93] If 2,6-dimethoxypyridine (DMP) was used instead of CuO in DCM/THF (4:1), a catalytic amount of the chiral titanium taddolate could still promote the transformation to afford bicyclic lactones **326** with 96–99% *ee* (Scheme 87).[94]

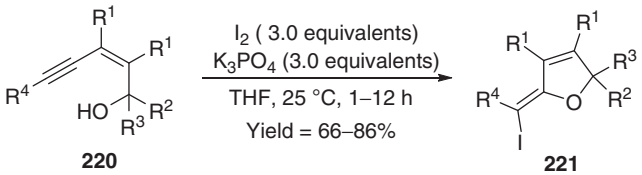
A stoichiometric amount of the binol-based phosphoramidite was used to induce enantioselectivity in the asymmetric iodocarbocyclization of alkadienyl or alkatrienyl arenes to afford the product **328** with up to 91% *ee* (Scheme 88).[95]



217 **218** **219**

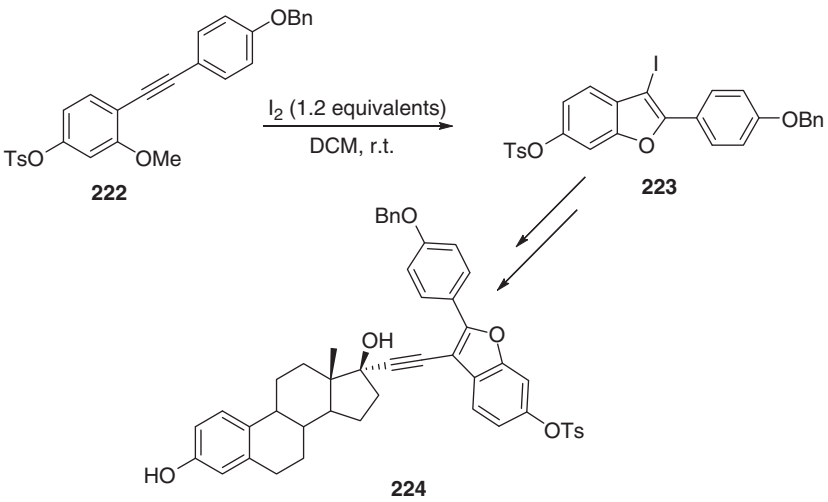
$R^1 = R^2$ = Ph (Yield = 60%)
R^1 = Ph; R^2 = Bu (Yield = 71%)
R^1 = Bu; R^2 = Ph (Yield = 77%)
R^1 = Me; R^2 = Ph (Yield = 88%)
R^1 = Me; R^2 = Bu (Yield = 65%)
R^1 = CO_2Me; R^2 = Ph (Yield = 47%)

Scheme 49



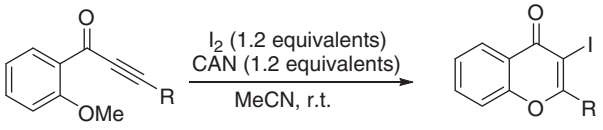
220 **221**

Scheme 50



222 **223** **224**

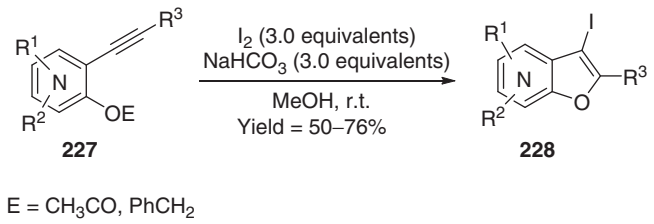
Scheme 51



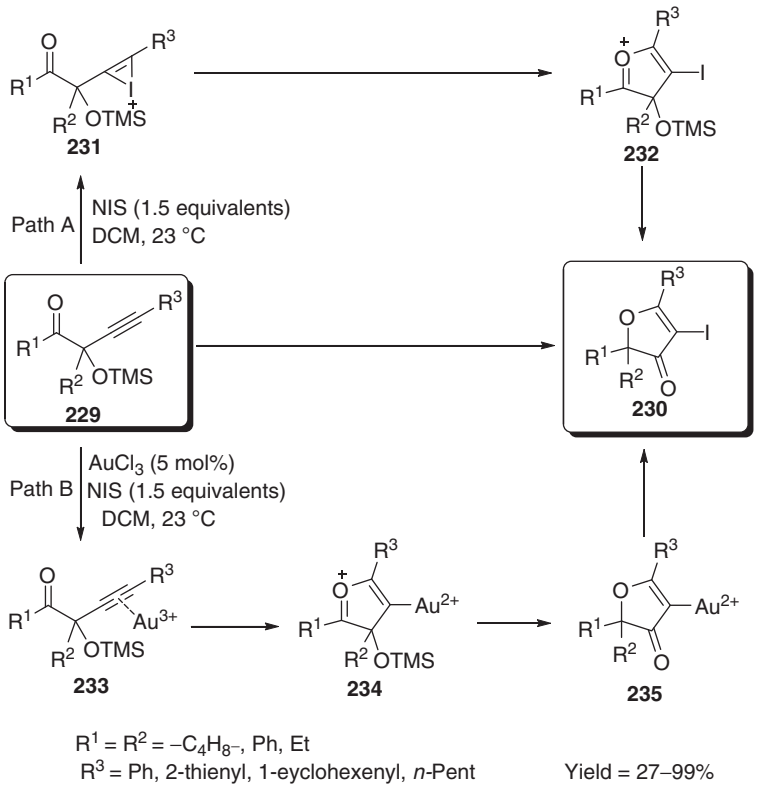
225 **226**

R = Ph — Yield = 97%
4-Me-C_6H_4 — 95%
Hexyl — 91%
4-MeO-C_6H_4 — 98%

Scheme 52



Scheme 53



Scheme 54

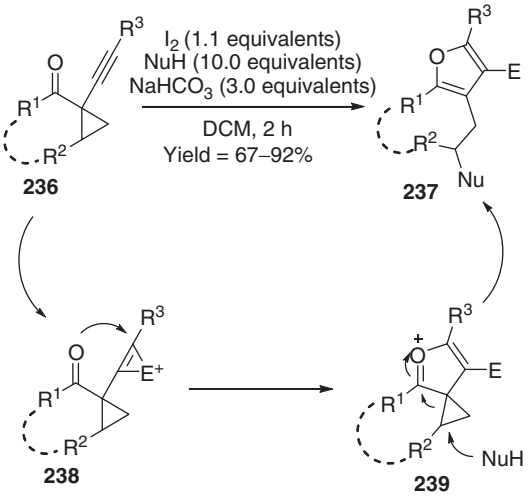
In the total synthesis of garsubellin A, Danishefsky and coworkers used iodocarbocyclization as the key step under the standard conditions in a 85% yield (Scheme 89).[96] Then the same group applied the I_2-induced electrophilic cyclization in the total synthesis of nemorosone and clusianone. A significant complication arose in the iodonium-induced carbocyclization reaction, shown in Scheme 90. Compounds **336** and **337** could be reconverted into **334** by treating them with zinc in aqueous THF in high yield.[97] In addition to the desired carbocyclization product **335** (obtained only in a 32% yield), substantial quantities (i.e., 50%) of a virtually 1:1 mixture of oxygen competitive products **336** and **337** were also obtained. Fortunately, both the oxygen competitive products could be reconverted into the starting material in a very high yield by the action of zinc in aqueous THF.

4.07.2.1.3.2 Cyclization involving alkynes

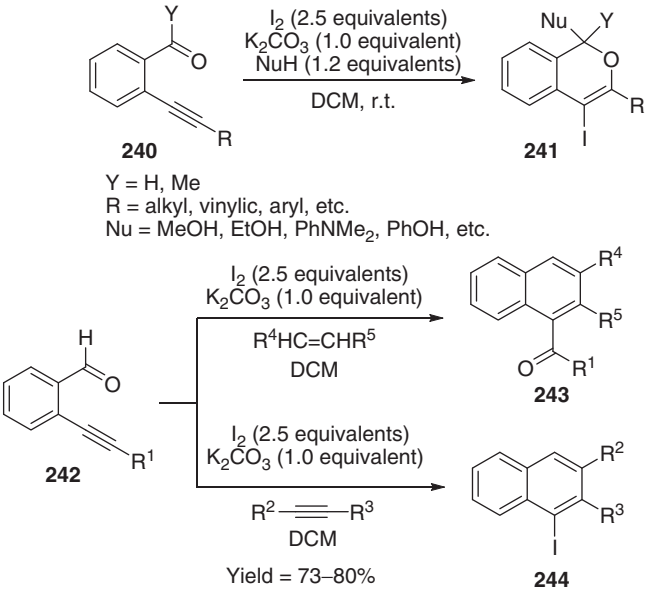
3-Iodo-1*H*-indene derivatives are synthesized by iodonium-promoted 5-*endo-dig* carbocyclization of 2-substituted ethynylmalonates (Scheme 91).[98]

If the substrate **340** was modified to **342,** both of 5-*exo-dig* and 6-*endo-dig* cyclization would be possible. Liang and coworkers reported a methodology for the synthesis of indene or naphthalene derivatives with high regio- and stereoselectivity under mild reaction conditions (Scheme 92).[99] The resonance and electronic effects force the carbon of the malonate group closer to C-1 or C-2 of the acetylenic malonates, leading to the formation of five- or six-membered ring.

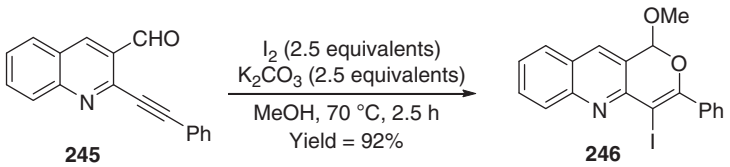
Electron-rich aryls are also a type of good C-nucleophiles. When aryl propargylic alcohols are used as substrates, diiodinated carbocycles and oxygen heterocycles can be readily synthesized (Scheme 93).[100] In the presence of protons, substrate **347** could lose a hydroxyl group to afford the propargylic carbocations intermediate, which is in resonance with allene cation **348**. Then



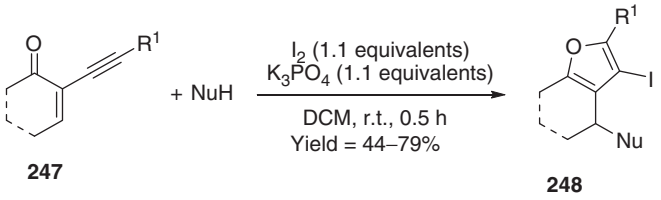
Scheme 55



Scheme 56

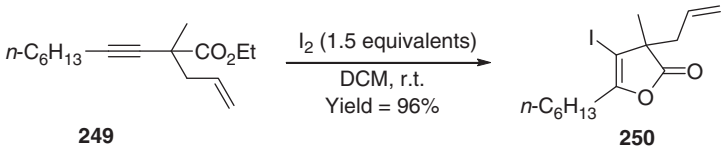


Scheme 57



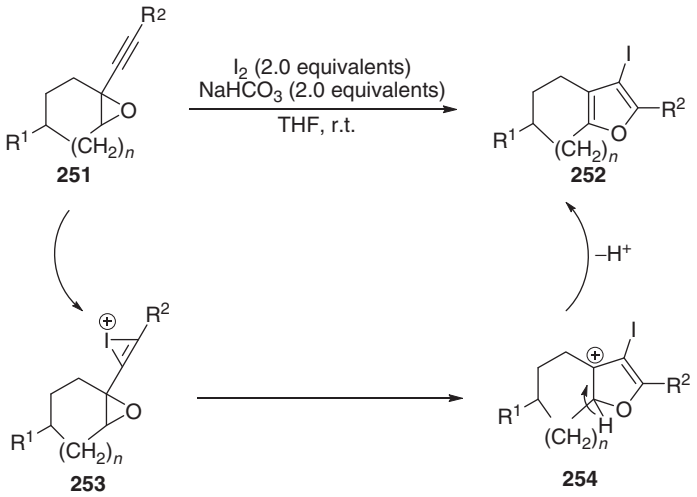
247 248

Scheme 58



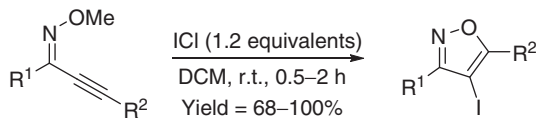
249 250

Scheme 59



251 252 253 254

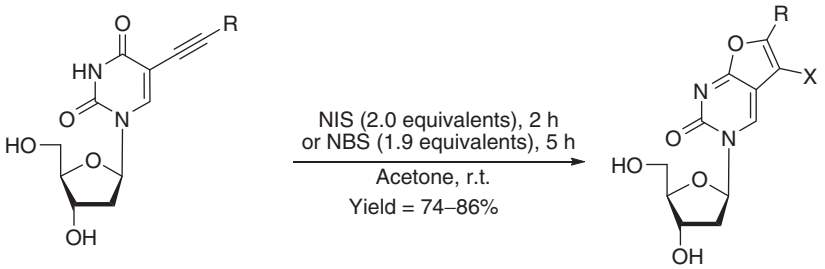
Scheme 60



255 256

R^1 = H, Me, Ar, *n*-C_6H_{13}, *t*-Bu, etc.
R^2 = Me, Ar, *t*-Bu, etc.

Scheme 61

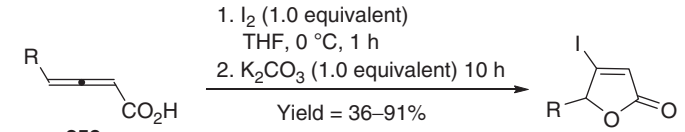


257

R = *p*-$CH_3C_6H_4$, *p*-$(CH_3)_3CC_6H_4$, *c*-C_3H_5

258

Scheme 62

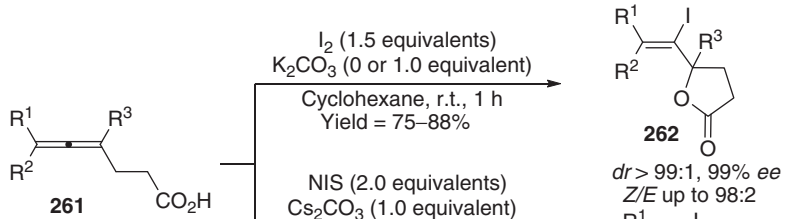


259

R = *n*-C_4H_9, *n*-C_7H_{15}

260

Scheme 63



261

R^1 = H, alkyl
R^2 = H, alkyl
R^3 = H, alkyl

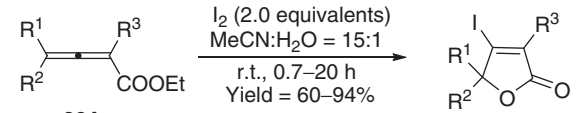
262

dr > 99:1, 99% *ee*
Z/*E* up to 98:2

263

>98% *ee*
Z/*E* up to 98:2

Scheme 64

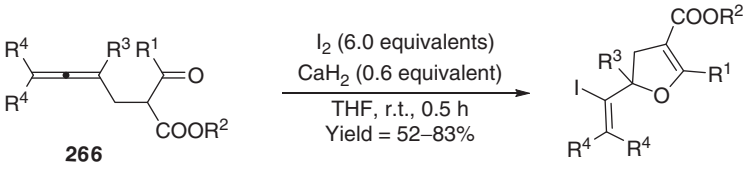


264

R^1 = alkyl, phenyl
R^2 = H, alkyl
R^3 = H, alkyl, benzyl

265

Scheme 65

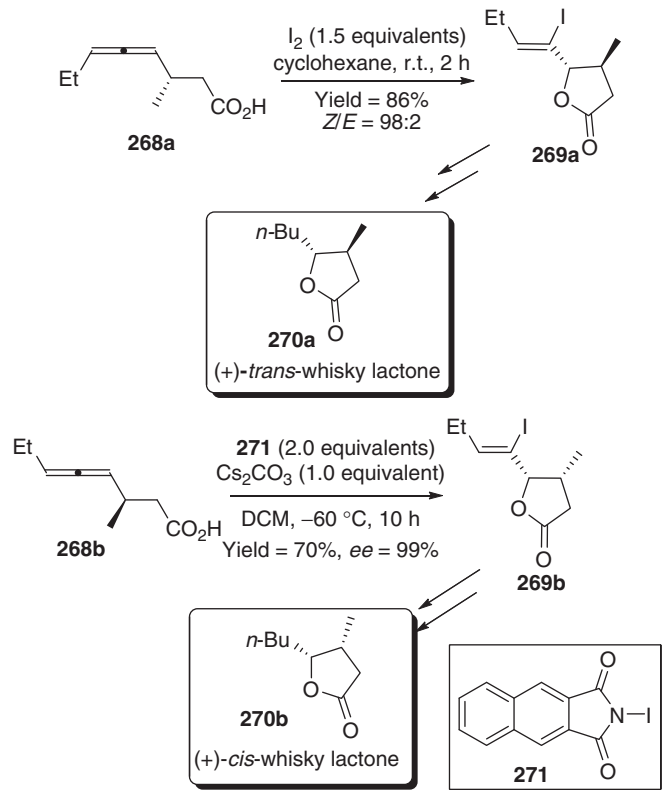


266

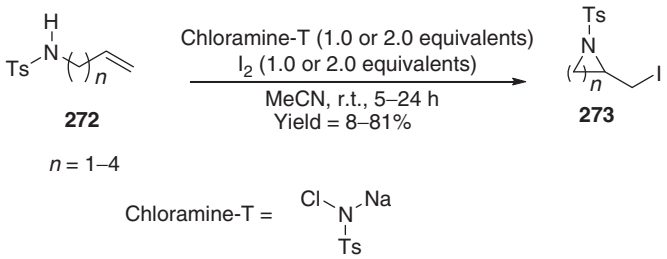
267

R^1 = Me, Et, *i*-Pr, Bn, Ph
R^2 = Et, Me
R^3 = H, Et, Bn
R^4 = H, Me, $(CH_2)_5$

Scheme 66



Scheme 67



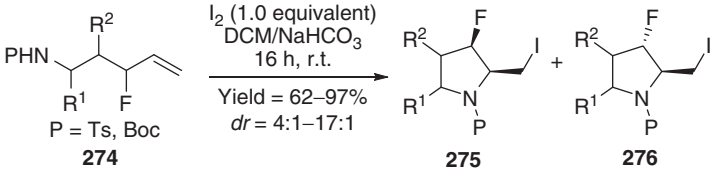
272

273

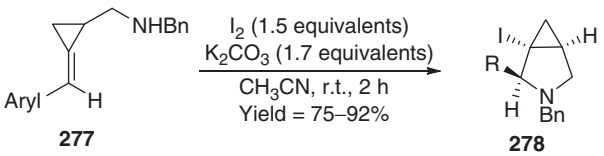
n = 1–4

Chloramine-T =

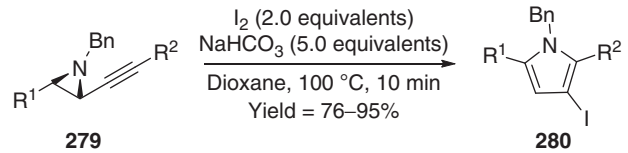
Scheme 68



Scheme 69

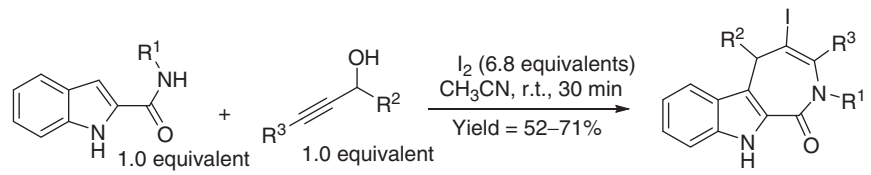


Scheme 70



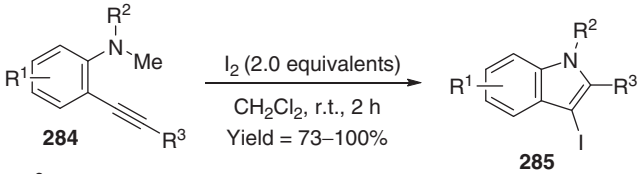
R^1 = alkyl, phenyl, 2-naphthyl
R^2 = alkyl, phenyl, benzyl

Scheme 71



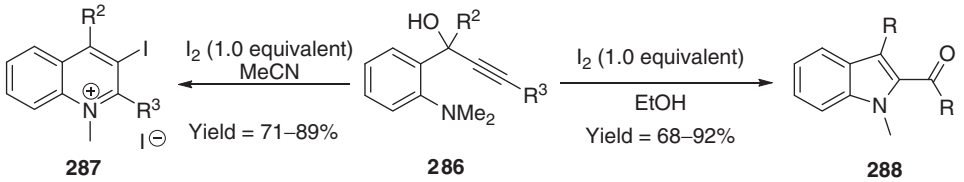
R^1 = alkyl, benzyl
R^2 = aryl
R^3 = aryl, alkyl

Scheme 72



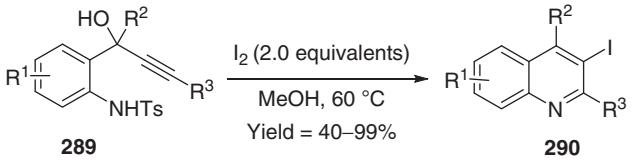
R^2 = Me, *n*-C_6H_{13}, Ph
R^3 = Ph, *n*-C_6H_{13}, *t*-Bu

Scheme 73



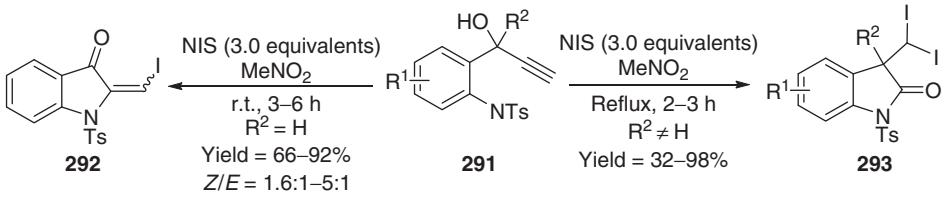
287 286 288

Scheme 74



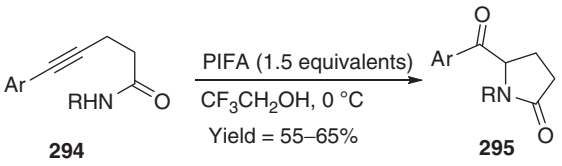
289 290

Scheme 75



292 291 293

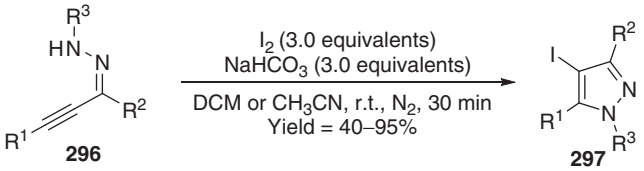
Scheme 76



294 295

Ar = Ph, *p*-MeOC$_6$H$_4$, 1-naphthyl, 2-thienyl
R = Ph, Bn, Me

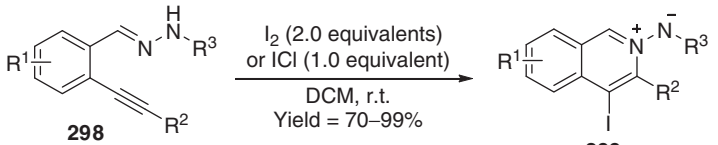
Scheme 77



296 297

R^1 = alkyl, aryl, heteroaryl, ferrocenyl
R^2 = H, methyl, phenyl
R^3 = alkyl, aryl

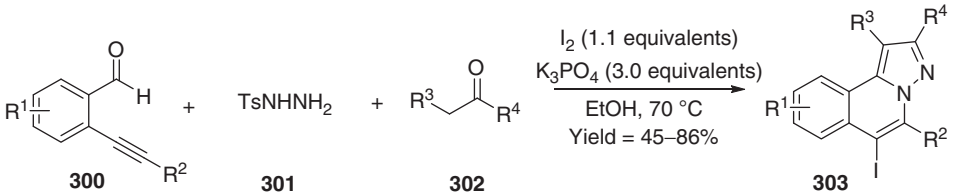
Scheme 78



298 **299**

R^1 = H, F, alkyloxyl
R^2 = phenyl, aryl, alkyl
R^3 = Ts, SO_2Ph, COPh

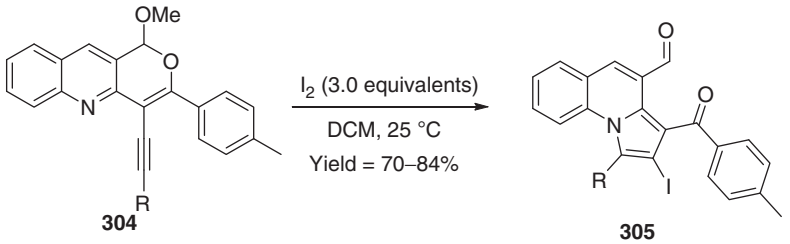
Scheme 79



300 **301** **302** **303**

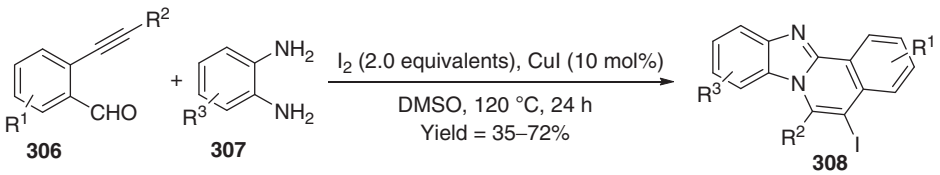
R^1 = H, Cl,F
R^2 = phenyl, alkyl
R^3 = alkyl, H
R^4 = alkyl, H

Scheme 80



304 **305**

Scheme 81



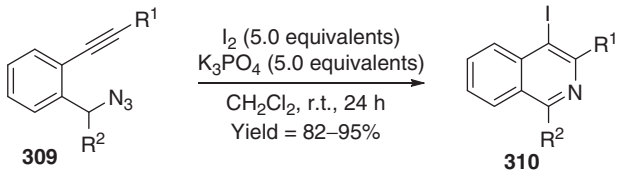
306 **307** **308**

R^1 = H, methyl, methyoxyl, Cl, F, formyl
R^2 = phenyl, alkyl, aryl
R^3 = H, methyl, Cl, CF_3

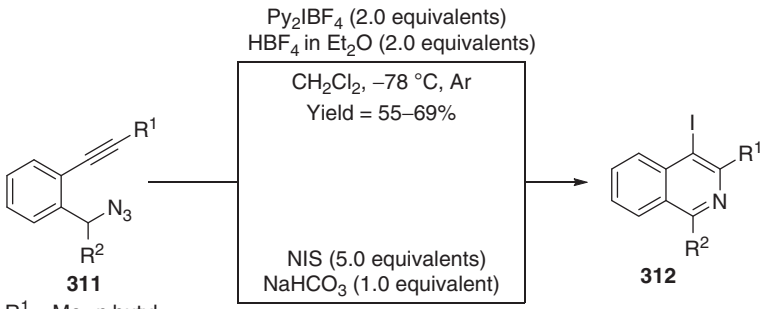
Scheme 82

intermediate **348** reacts with an iodide anion to give allenyl iodide **349**, which can be further activated by an iodide cation. Then it is attacked by phenyl to produce the diiodinated product **350**.

The Larock group developed a series of methodologies for the synthesis of quinoline, naphthalene, and 2*H*-benzopyran derivates using electrophilic cyclization via the electron-rich aryl as nucleophile (Scheme 94).[101]

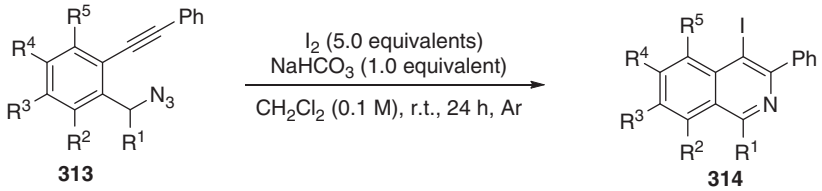


R^1 = Ph, *p*-OMePh, 1-cyclohexenyl
R^2 = H



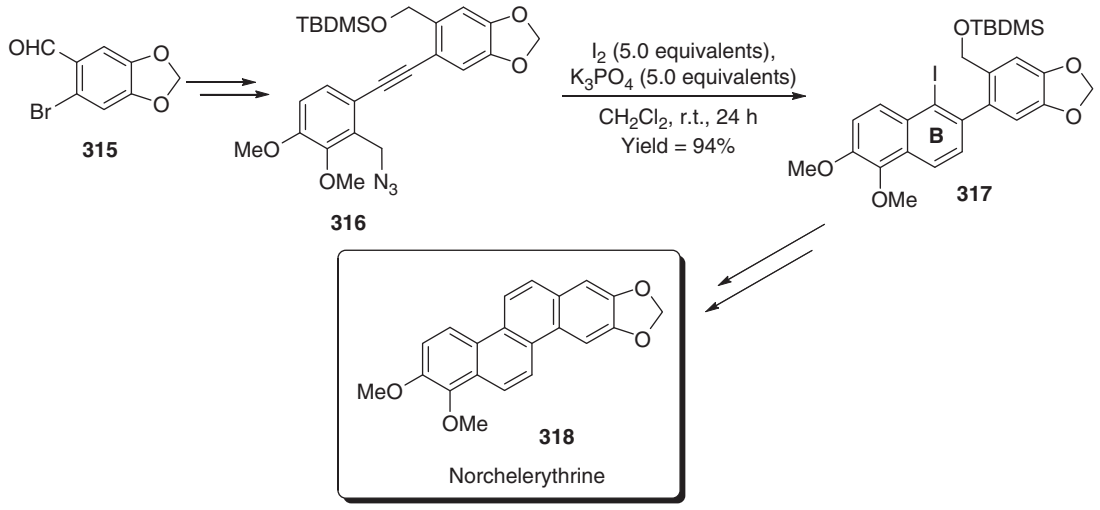
R^1 = Me, *n*-butyl, *t*-butyl, CH_2TMS
R^2 = H

Scheme 83

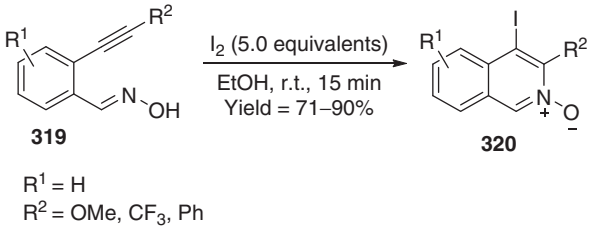


R^1 = Me, R^2 = H, R^3 = H, R^4 = H, R^5 = H — Yield = 69%
R^1 = *n*-hexyl, R^2 = H, R^3 = H, R^4 = H, R^5 = H — Yield = 73%
R^1 = cyclopropyl, R^2 = H, R^3 = H, R^4 = NO_2, R^5 = H — Yield = 72%

Scheme 84



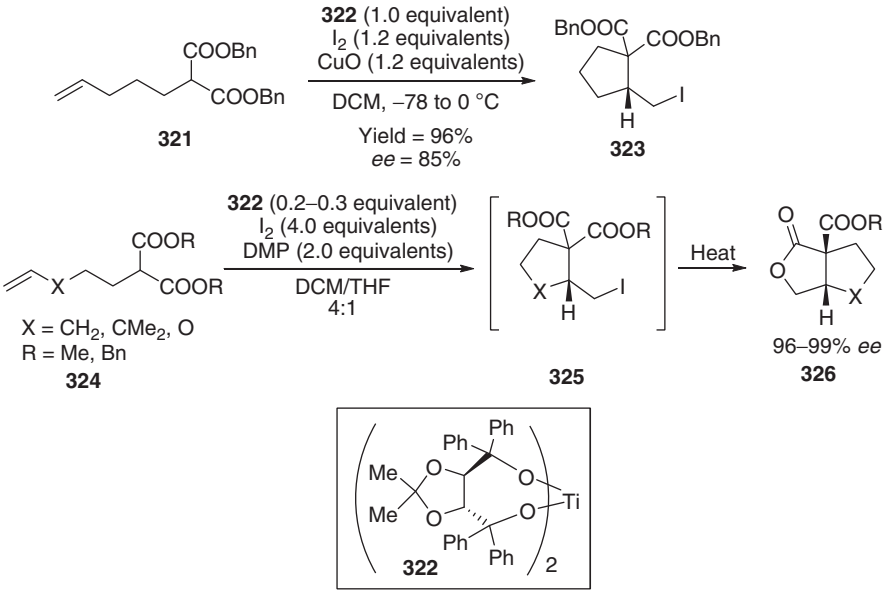
Scheme 85



319 **320**

R^1 = H
R^2 = OMe, CF_3, Ph

Scheme 86



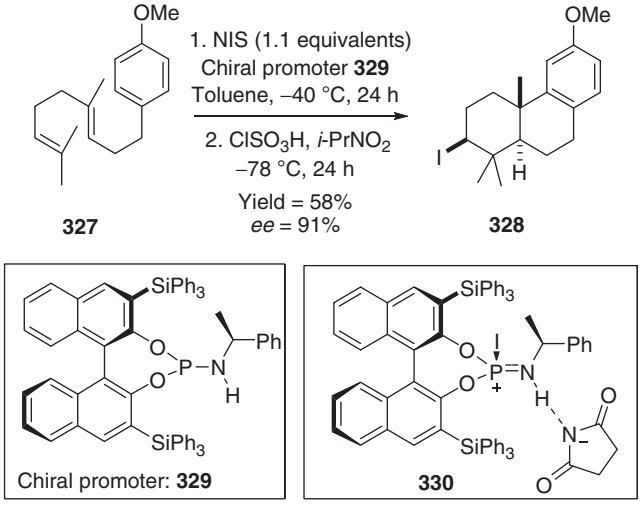
321 **323**

324 **325** **326**

96–99% *ee*

322

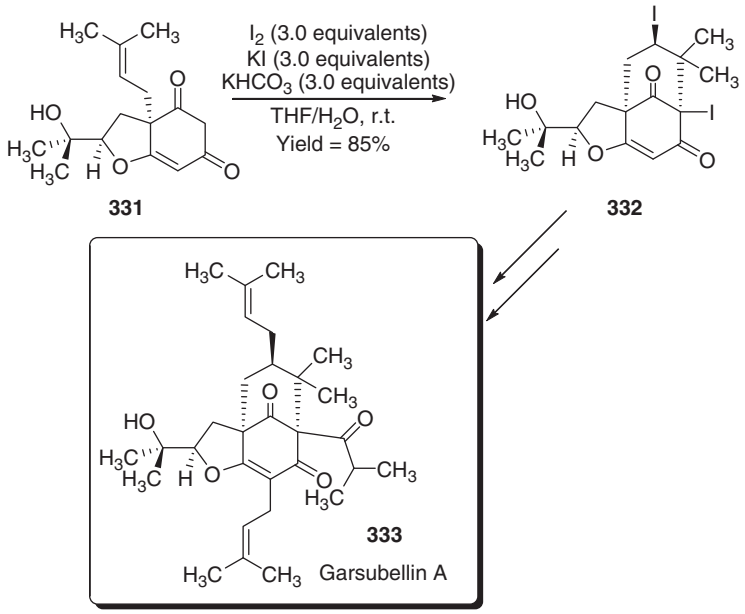
Scheme 87



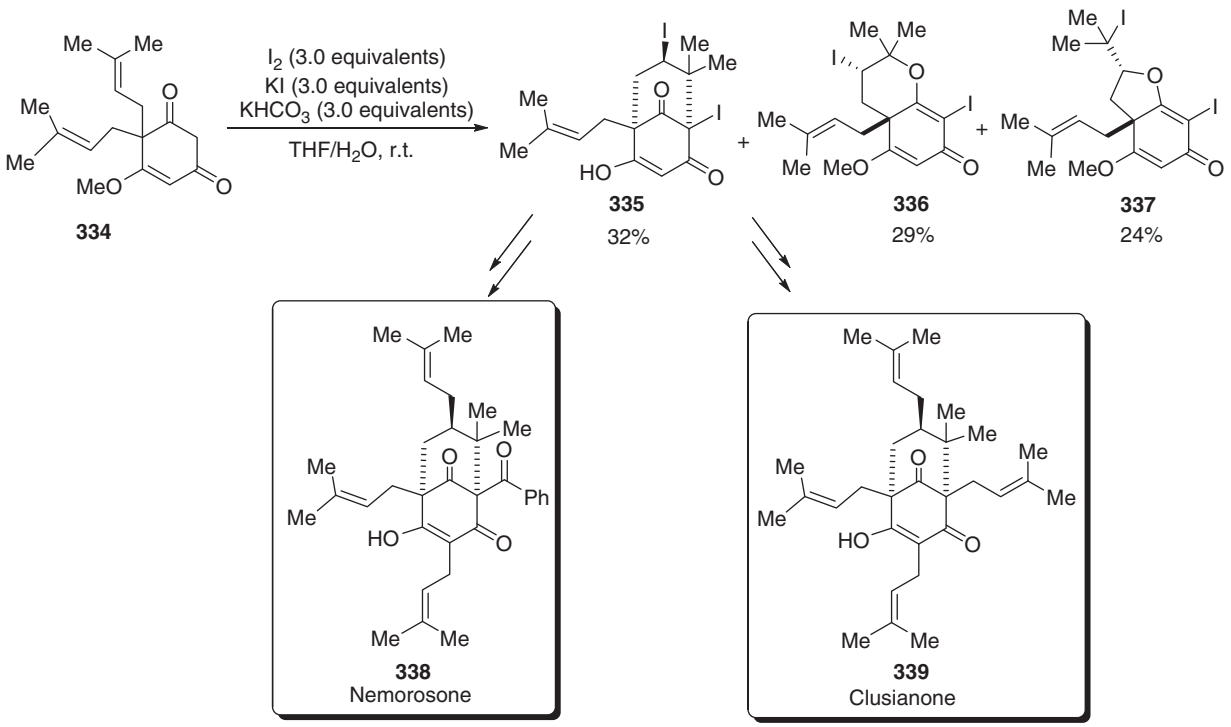
327 **328**

330

Scheme 88



Scheme 89

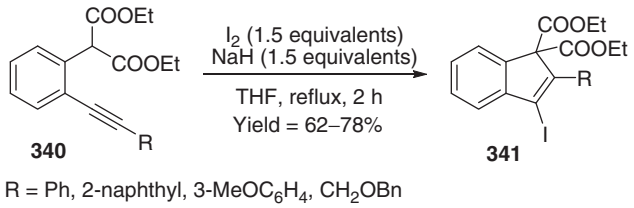


Scheme 90

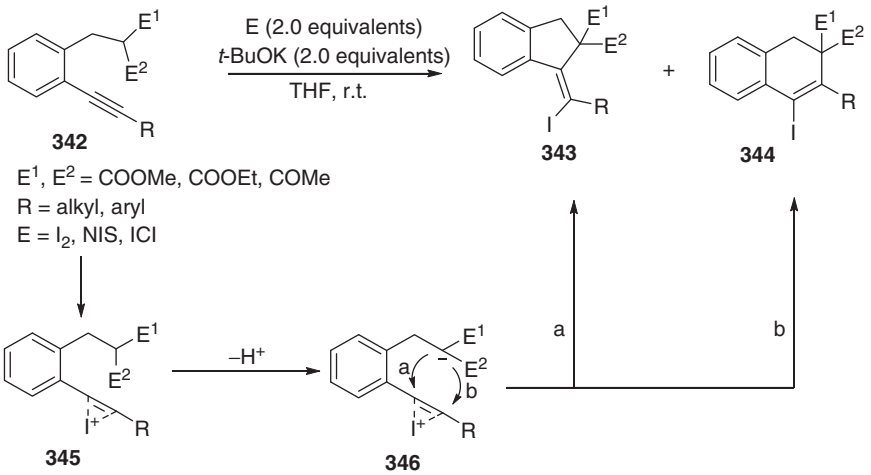
Yamamoto and coworkers have developed an efficient and general iodine-mediated electrophilic cyclization for the synthesis of 2,3-diiodo-dihydronaphthalenes from aryl propargyl alcohols (Scheme 95).[102]

Li's group described an example that 4-(*p*-methylaryl)-1-alkynes could undergo the intramolecular *ipso*-iodocyclization process with ICl or I_2 to afford the corresponding 8-methylene-1-azaspiro[4,5]trienes in moderate to good yields (Scheme 96).[103]

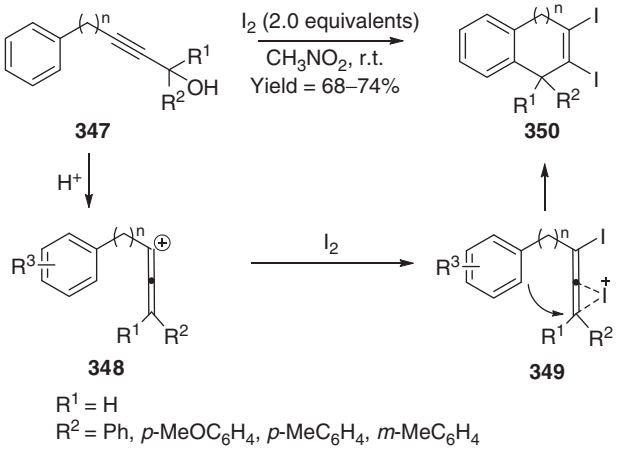
Four different types of fused arenes, fluoranthene, indeno-[2,1-α]phenalene, (8*H*)cyclopenta[α]acenaphthylene, and pyridine[α]acenaphthylene, were efficiently constructed through iodine-mediated electrophilic cyclizations of 1,8-dialkynyl naphthalenes in a single step (Scheme 97).[104]



Scheme 91



Scheme 92

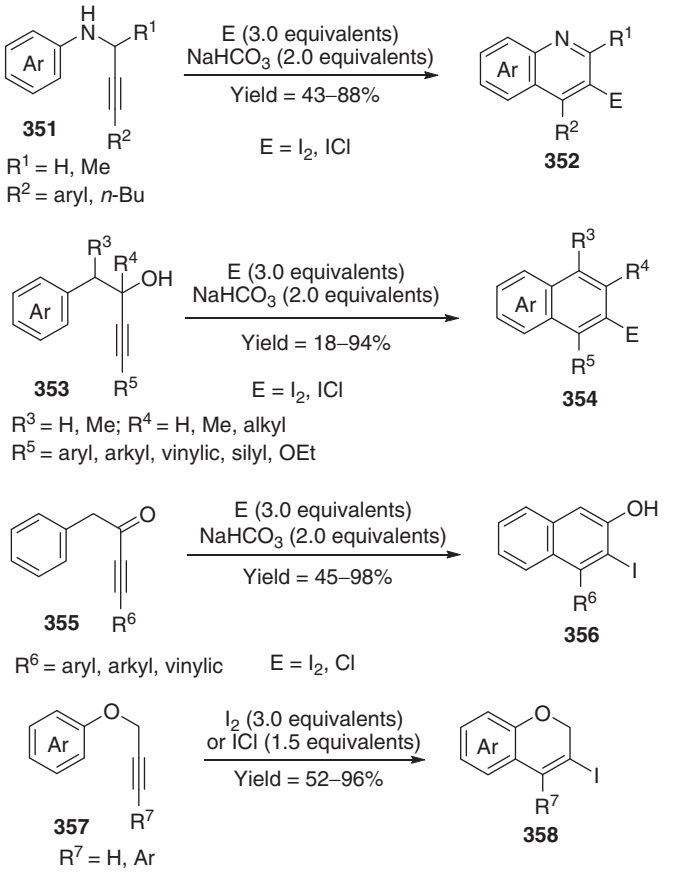


Scheme 93

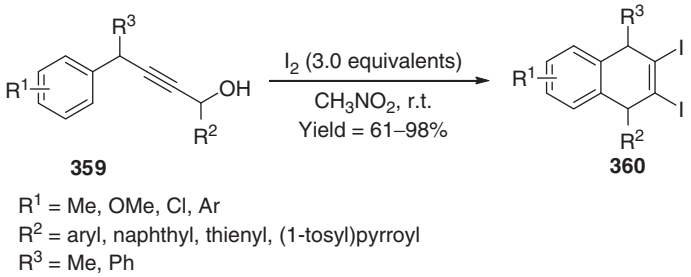
Kirsch et al. investigated the reactivity of 1,5-enynes and 1,6-enynes in the presence of electrophilic iodine sources (Scheme 98).[105] 1,5-Enynes favored the formation of six-membered carbocycles with great structural diversity, whereas 1,6-enynes favored the more rapid 5-*exo* cyclization yielding the corresponding five-membered carbocycles in moderate to good yields.

Wang and coworkers developed a methodology to assemble the azaanthraquinone and diazaanthraquinone skeletons from *N*-propargylaminoquinones by utilizing an iodine-induced 6-*endo-dig* electrophilic cyclization (Scheme 99).[106]

With $Cu(OTf)_2$, 3-alkylation of indole resulted in the formation of 3-propargylic indole, which could be further converted into 2-iodo-1,4-dihydrocyclopenta[*b*]indoles in the presence of NIS and boron trifluoride etherate (Scheme 100).[107]



Scheme 94



Scheme 95

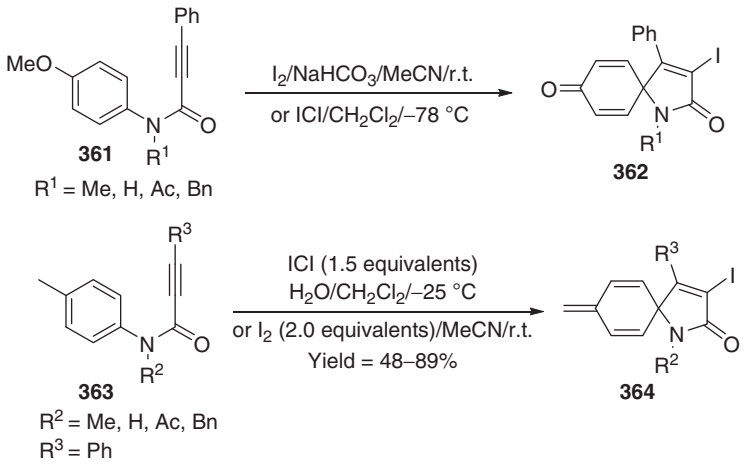
4.07.2.1.4 S *or* Se*-nucleophiles*

An efficient synthesis of 3-halo-chalcogenophene[3,2-*c*]chromene has been accomplished via electrophilic cyclization reaction of 3-alkynyl-4-chalcogen-2*H*-chromene (Scheme 101).[108]

Zeni's group presented the electrophilic cyclization reactions of 3-alkynylthiophenes, which proceeds cleanly under mild reaction conditions, and gives fused 4-iodoselenophene-[2,3-*b*]thiophenes in excellent yields (Scheme 102).[109]

Zeni et al. developed an efficient method for the synthesis of tetrahydroselenophene derivatives by electrophilic cyclization of 1-butylseleno-4-alkynes. The cyclized 5-*exo-dig* products were obtained in high yields under mild conditions (Scheme 103).[110]

A formal total synthesis of the benzothiophene selective estrogen receptor modulator (SERM) desketoraloxifene analogs has been accomplished from alkynes bearing electron-rich aromatic rings by electrophilic cyclization using I_2 (Scheme 104).[111] Compound **392** could be converted to oxygen-bearing 3-iodobenzo[*b*]thiophenes in excellent yields via a two-step approach involving Suzuki–Miyaura coupling and Mitsunobu reactions.



Scheme 96

4.07.2.2 Bromocyclization

4.07.2.2.1 Cyclization involving alkenes

Oxetanes can be obtained in good yields from cinnamyl alcohols using bis(collidine) bromine(I) hexafluorophosphate as electrophile (Scheme 105).[112] It is an efficient way to get Oxetin (oxetan-2-carboxylic acid), which is a natural product possessing antibiotic activities. It is developed by the same group that developed silicon-directed 4-*exo-rig* electrophilic cyclizations of homoallylic alcohols to prepare oxetanes (Scheme 106).[113]

Shi and coworkers reported that various γ-hydroxyalkenes and γ-amino-alkenes could efficiently undergo bromocyclization using NBS as the Br^+ source with chiral phosphoric acid **401** as the catalyst, giving 2-substituted THFs and tetrahydropyrroles with generally good yields and up to 91% *ee* (Scheme 107).[114]

Fujioka and coworkers reported an example of asymmetric bromolactonization of 5-substituted 5-hexenoic acids catalyzed by a C3-symmetric chiral trisimidazoline (Scheme 108).[115] The use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) instead of NBS as the bromine source could increase the selectivity, although the conversion was moderate when 0.6 equivalent was used. With 1.0 equivalent of DBDMH, the reaction proceeds in a high yield with good selectivity.

Yeung and coworkers developed an *S*-alkyl thiocarbamate catalyst for the same reaction with high yields and good *ee*s (Scheme 109).[116] Very recently, Yeung et al. developed the first organocatalytic halolactonization of unsaturated carboxylic acids using zwitterionic catalyst **411** and stoichiometric *N*-bromosuccinimide halogen source, resulting in the formation of medium-sized lactones (Scheme 110).[117]

The Tang group recently discovered a DABCO-catalyzed *syn*-selective 1,4-bromolactonization of enynes. This reaction gave axially chiral allenes as the main products.[118] In 2010, the same group described the mechanism that catalyst **413** (which has a bridgehead nitrogen similar to DABCO) promotes highly enantioselective bromolactonization of 2-enynes **412** and **415** to give bromoallenes **414** and **416** (Scheme 111).[119]

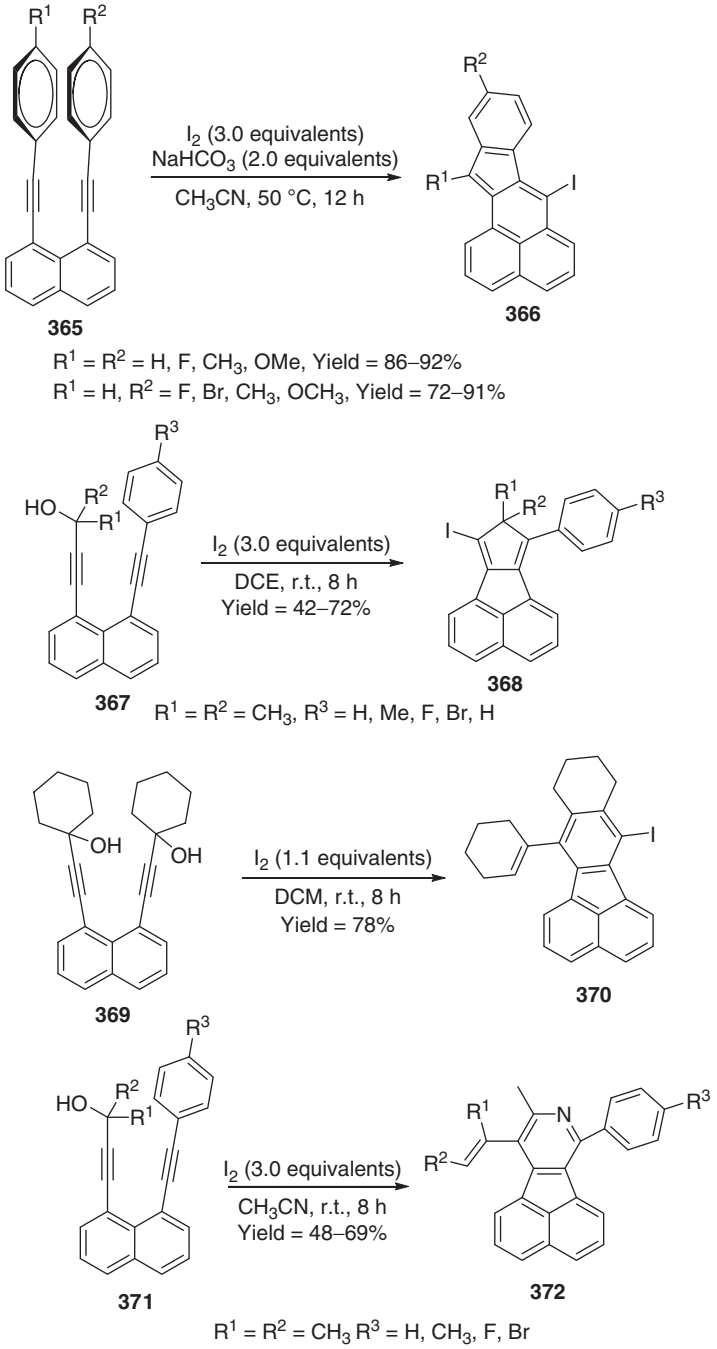
A facile, efficient, and enantioselective approach toward 4-bromo-3-aryl-3,4-dihydroisocoumarins through an amino-thiocarbamate-catalyzed bromocyclization process has been developed by Yeung's group (Scheme 112).[120] This method is used for the synthesis of biologically important 3-substituted 3,4-dihydroisocoumarins and its related compounds.

Very recently, Martin and coworkers reported a novel bifunctional catalyst from BINOL to accelerate highly efficient and enantioselective bromolactonizations of unsaturated acids (Scheme 113).[121] These reactions represent the first catalytic bromolactonizations of alkylsubstituted olefinic acids to give lactones via 5-*exo* mode cyclizations, and the new carbon–bromine bonds are formed at the stereogenic center with high enantioselectivity. Also a tentative stereochemical model for enantioselective bromolactonizations is proposed (Scheme 114).

Fujioka and coworkers applied the asymmetric bromolactonization of 5-substituted 5-hexenoic acids catalyzed by a C3-symmetric chiral trisimidazoline in the total synthesis of tanikolide (Scheme 115).[115b]

Snyder and coworkers developed simple reagents such as **432,** for direct halonium-induced polyene cyclizations.[122] Electron-rich and -deficient terpenes derived from geraniol, farnesol, and nerol could be used for the synthesis of a diverse array of complexes with chlorine-, bromine-, and iodine-containing polycyclic frameworks. Total synthesis of many natural products are achieved with this protocol, such as peyssonol A, peyssonoic acid A (Scheme 116), and formal racemic total syntheses of aplysin-20, loliolide, and K-76.

Treatment of γ-disubstituted β,γ-unsaturated hydroxamates with bis(collidine)bromine(I) hexafluorophosphate led mainly to the formation of cyclic bromo imidates – the thermodynamic products (Scheme 117).[123]

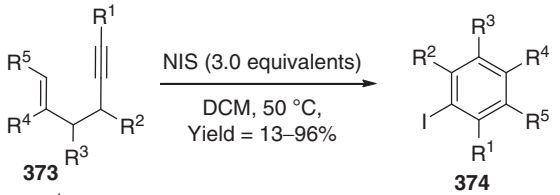


Scheme 97

In the total synthesis of (+)-chaetocin, bromocyclization induced by NBS is used in the assemblage of the five-membered ring, which affords the desired product **448** in 88% yield (Scheme 118).[124] This reaction was highly stereoselective, and no appreciable amount of the other stereoisomer was detected.

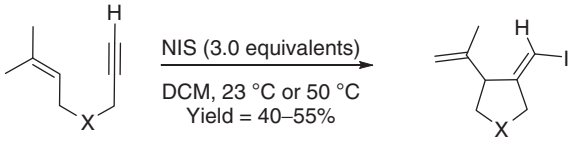
Lera and coworkers have developed a versatile synthetic route leading to WIN 64821 (**452**) and WIN 64745 (**453**) (Scheme 119).[125,126] Bromohexahydropyrroloindole **451** could be easily achieved from commercial *D*-tryptophan via stereoselective bromocyclization of the tryptophan derivative **450** in the presence of *N*-bromosuccinimide, according to the methodology recently developed by the same group.[126]

In the asymmetric total synthesis of loline alkaloids, the Trauner group used bromine-induced electrophilic cyclization to construct the key ring (Scheme 120).[127] It goes through an unprecedented transannular aminobromination, which converts an eight-membered cyclic carbamate into a bromopyrrolizidine.



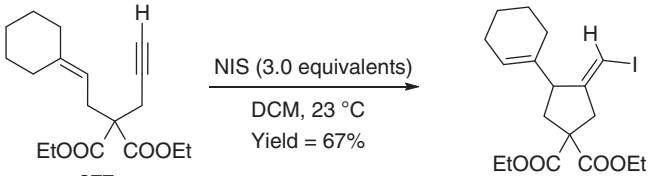
373 **374**

R^1 = Ar, H, Me, Br, alkene
R^2 = H, Me
R^3 = TIPSO$(CH_2)_3$, Me, Ph, alkyl
R^4 = Me, Ph, alkyl
R^5 = H, Me



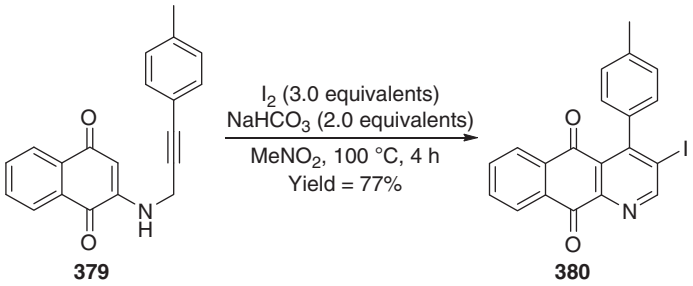
375 **376**

X = $(MeO_2C)_2C$, $(PhO_2S)_2C$, O, NTs



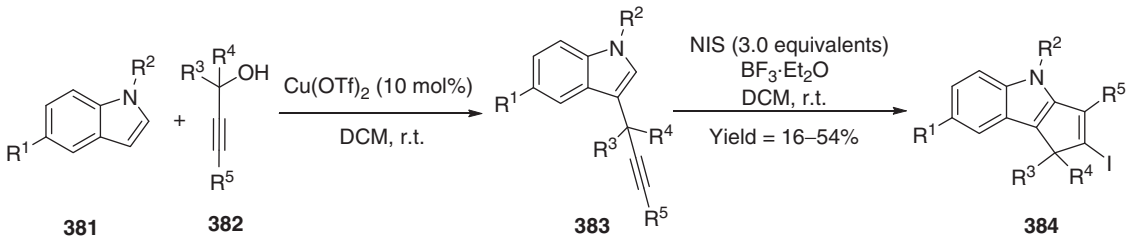
377 **378**

Scheme 98



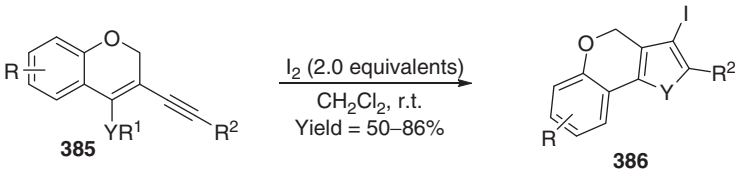
379 **380**

Scheme 99



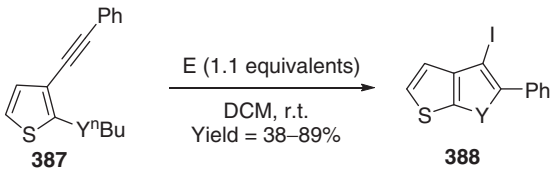
381 **382** **383** **384**

Scheme 100



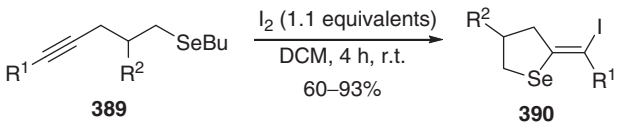
Y = S, Se; R = aryl, alkyl; R^1 = Me, butyl; R^2 = alkyl, aryl, alcohol

Scheme 101



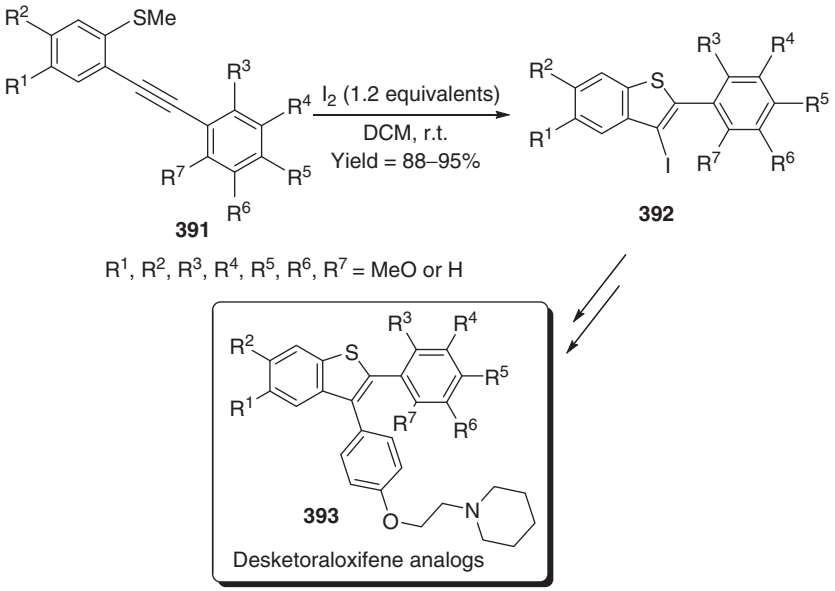
Y = Se, Te; E = I_2, ICl

Scheme 102

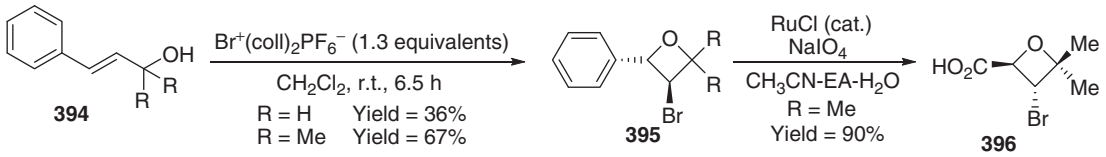


R^1 = aryl, heteroaryl, alkyl, SeBu, $Si(CH_3)_3$, propargyl alcohol
R^2 = H, OH, OBz

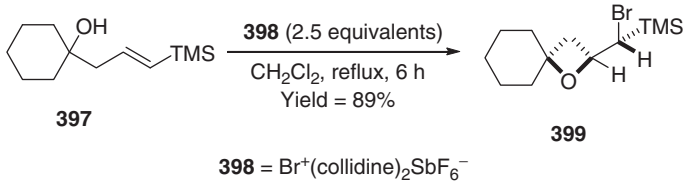
Scheme 103



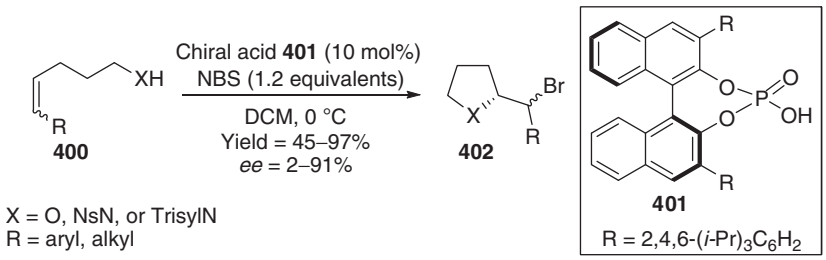
Scheme 104



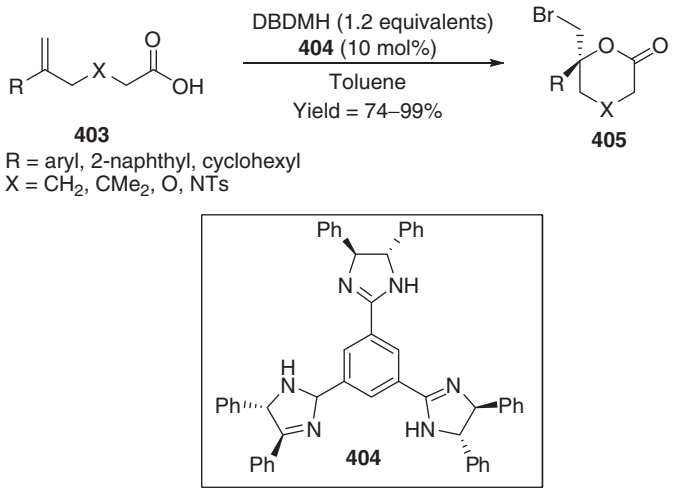
Scheme 105



Scheme 106

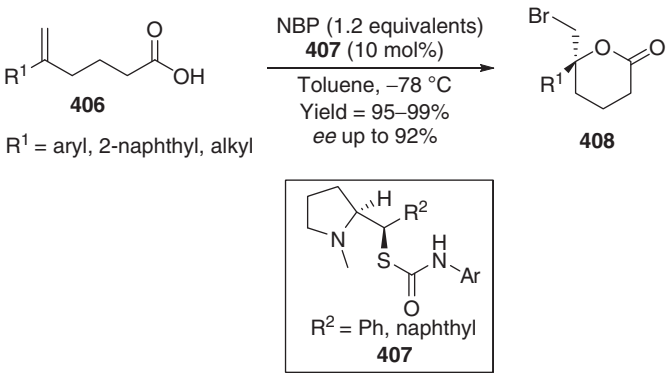


Scheme 107

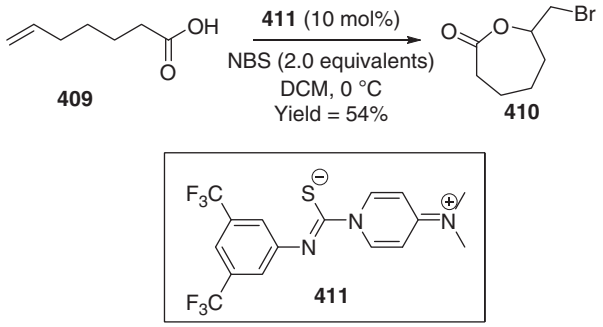


Scheme 108

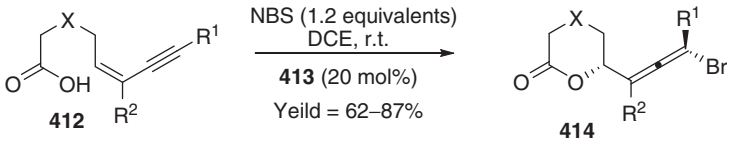
In the synthesis of pallidol, ampelopsin F, paucifloral F, and diptoindonesin A, Snyder and coworkers used bromine-induced electrophilic cyclization as a key step (Scheme 121).[128] Take pallidol as an example; a possible pathway of the bromocyclization induced by Br_2 is proposed in Scheme 121.

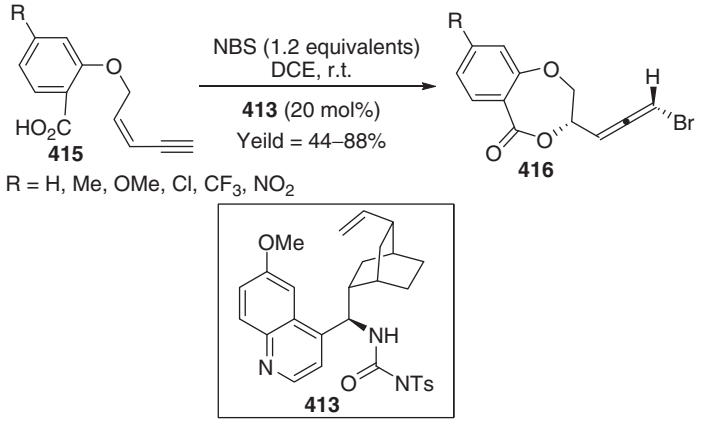


Scheme 109

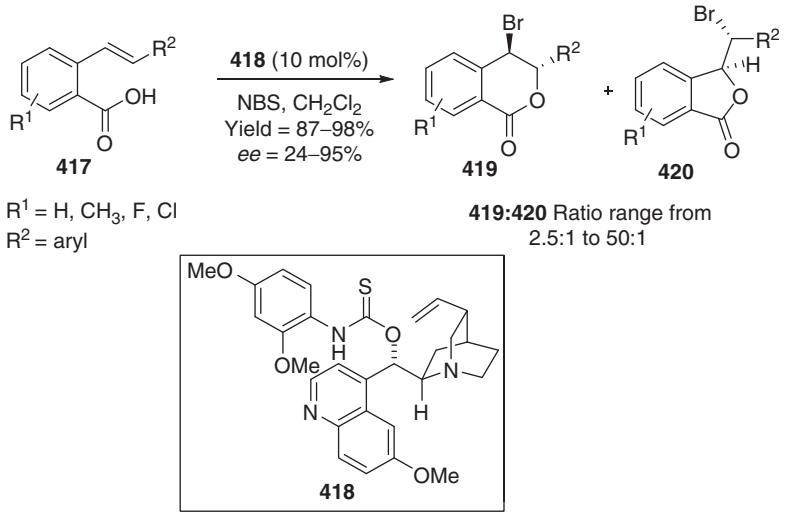


Scheme 110

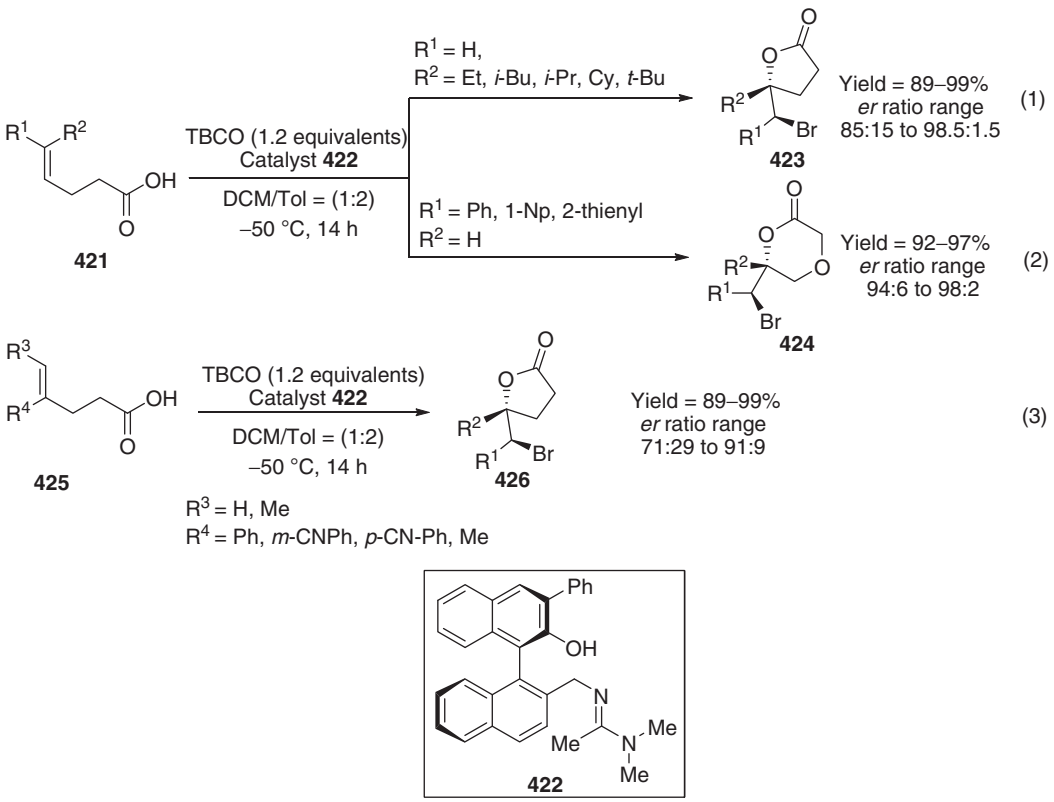




Scheme 111



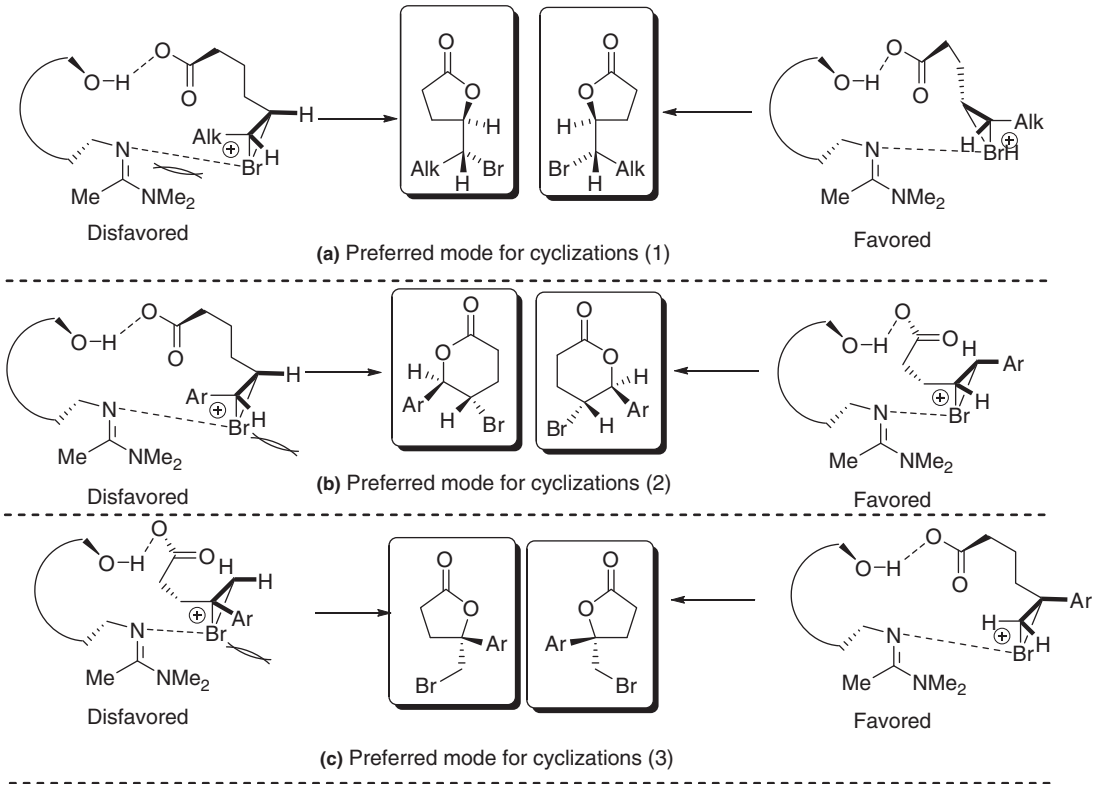
Scheme 112



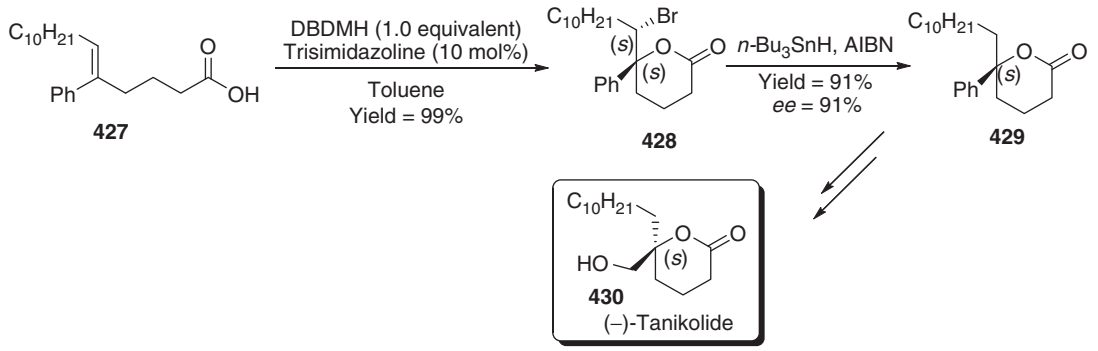
Scheme 113

4.07.2.2.2 Cyclization involving alkynes

Wu and coworkers developed an efficient route for the synthesis of isoquinoline-based azomethine ylides from 2-alkynylbenzaldoximes, DMAD, and bromine via tandem electrophilic cyclization-[3 + 2] cycloaddition-rearrangement reactions (Scheme 122).[129] When the DMAD is replaced by carbodiimide derivates, this process affords functionalized 1-amino-4-bromoisoquinolines in high yields (Scheme 123).[130] Then two efficient methods for the synthesis of functionalized *H*-pyrazolo[5,1-*a*]isoquinolines are developed subsequently, shown in Schemes 124.[87,131]



Scheme 114

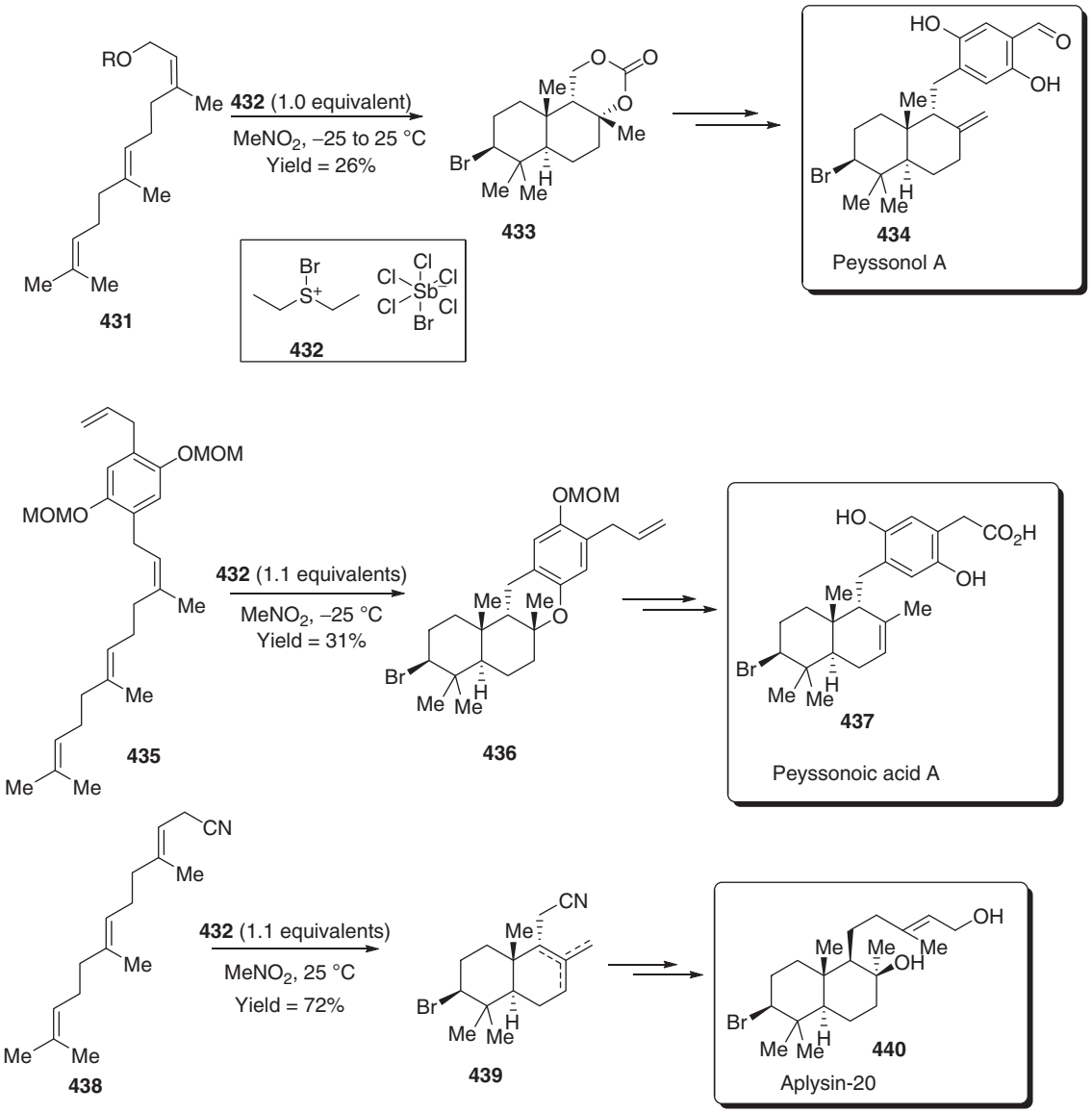


Scheme 115

In the synthesis of α-saxitoxinol, an analog of saxitoxin, Nishikawa and coworkers used the key bromocyclization reaction and subsequent intramolecular *N*-alkylation to construct a dibromomethylene intermediate **476** on treatment of **475** with pyridinium tribromide ($PyHBr_3$) at room temperature (Scheme 125).[132] Then another six steps were carried out to give α-saxitoxinol.

4.07.2.2.3 Cyclization of allenes

Vanadium bromoperoxidase is an enzyme present in marine algae, which catalyzed electrophilic halogenation reactions using hydrogen peroxide to oxidize and thereby activate bromide ion. Butler and coworkers well summarized the examples of vanadium bromoperoxidase in the biosynthesis of halogenated marine natural products.[133] Ma and coworkers reported the studies on electrophilic reaction of tertiary 2,3-allenols with NBS in H_2O or aqueous MeCN (Scheme 126).[134] It provides an efficiently selective method for the synthesis of 3-bromo-2,5-dihydrofurans.



Scheme 116

4.07.2.2.4 Cyclization of cyclopropane

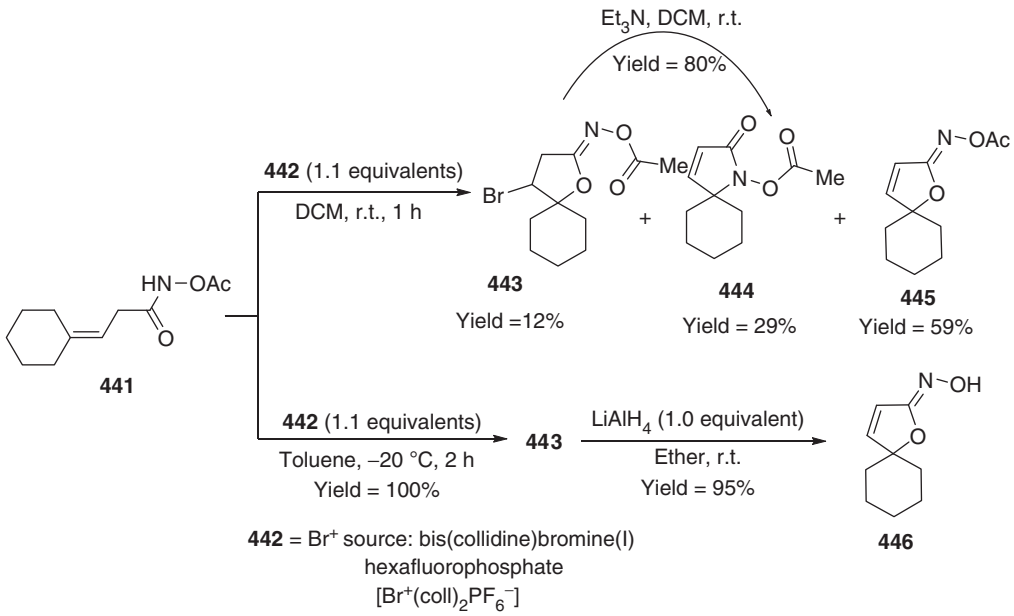
Highly efficient C–O bond formation has been developed via carboxylic acid catalyzed reaction of 1-acetylcyclopropanecarboxamides with NBS, which provides strategically novel and atom-economic access to biologically important 5-amino-3(2*H*)-furanones (Scheme 127).[135]

4.07.2.3 Chlorocyclization

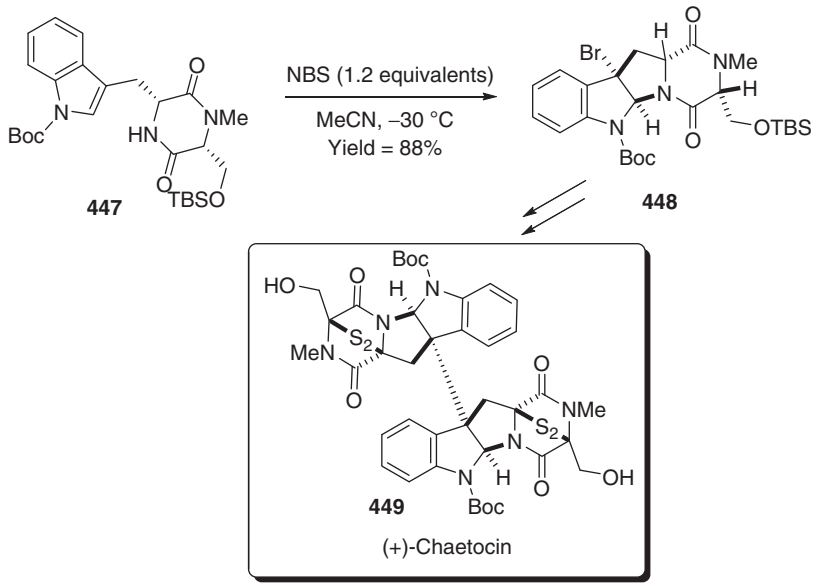
Iodocyclization and bromocyclization have been extensively investigated, and numerous electrophilic reagents have been developed. However, the research on chlorocyclization is not as many as that on the former two. The reason is partially due to the highly reactive nature of chloronium ions, which might exist in equilibrium with the corresponding carbocation rather than exclusively as cyclic chloronium ions. Thus, it makes chlorocyclization a formidable challenge for stereoselectivity control.[136] So far, a lot of Cl^+ reagents have been used for chlorocyclization, such as NCS, DCDMH, TCCA, chloramine-T, and DCDPH.

4.07.2.3.1 Cyclization involving alkenes

Borhan and coworkers reported catalytic enantioselective chlorolactonization of exocyclic 4-substituted pentenoic acids mediated by $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ and DCDPH (1,3-dichloro-5,5-diphenylhydantoin).[137] When the acid substrates were selected to react in $CHCl_3$-hexane in the presence of benzoic acid, the corresponding chlorolactones were obtained in high



Scheme 117

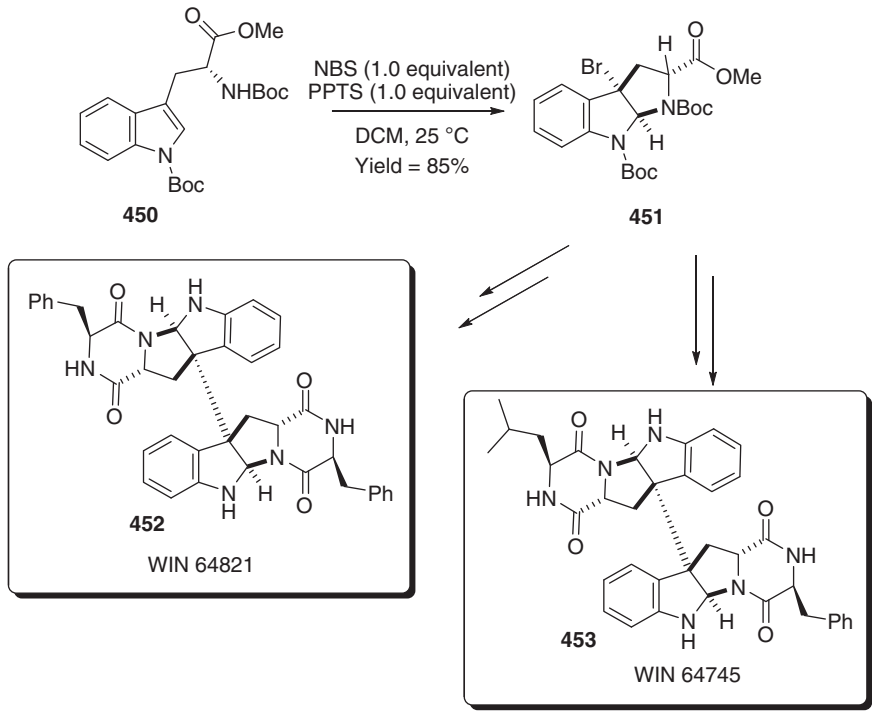


Scheme 118

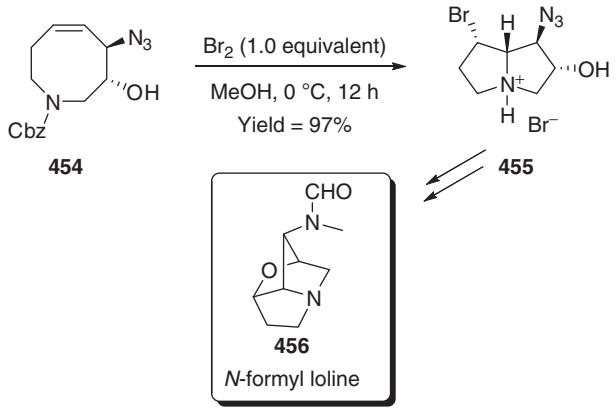
enantioselectivities (Scheme 128). Then they developed another highly stereoselective chlorocyclization of unsaturated amides to chiral heterocycles mediated by catalytic amounts (1–2 mol%) of commercially available $(DHQD)_2PHAL$ (Scheme 129).[138] The reaction is simply handled without strictly anhydrous or inert reaction conditions. The reaction scope is fairly general with regard to the substitution pattern of the olefin.

4.07.2.3.2 Cyclization involving alkynes

The 5-*endo-dig* chlorocyclization of 1,4-disubstituted alk-3-yn-1-ones (propargylic ketones) with trichloro-striazinetrione (trichloroisocyanuric acid, TCCA; 0.4 equivalent) in toluene at room temperature in the absence of base was developed, which provided 2,5-disubstituted 3-chlorofurans in high yields (79–96%) (Scheme 130).[139]



Scheme 119



Scheme 120

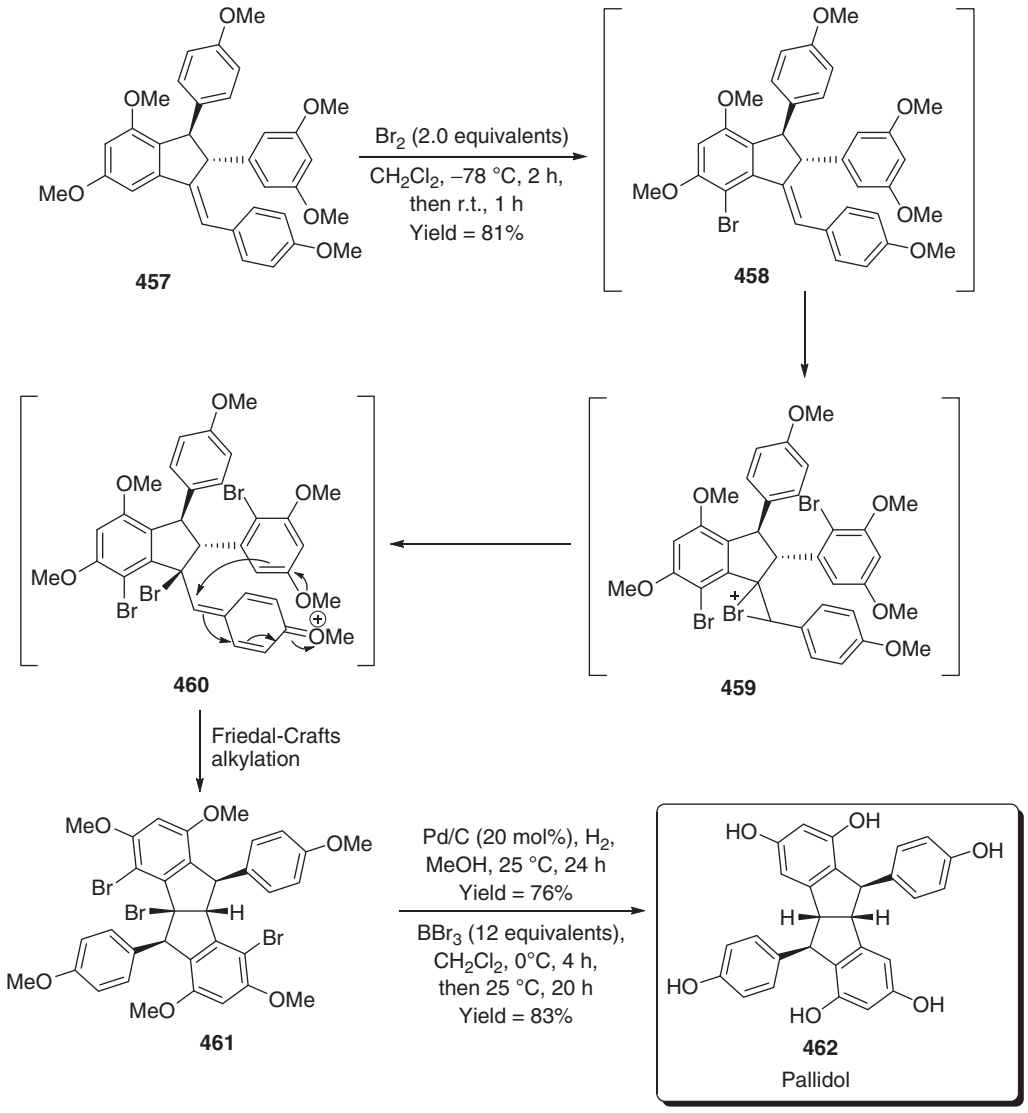
4.07.2.4 Fluorocyclization

Although fluorinated molecules widely exist in pharmaceuticals and agrochemicals,[140] the development of fluorocyclization reactions is not too many. The low reactivity of commonly used N-F electrophilic fluorinating reagents is particularly restrictive in the fluorocyclization. This section summarizes the progress in fluorocyclization.

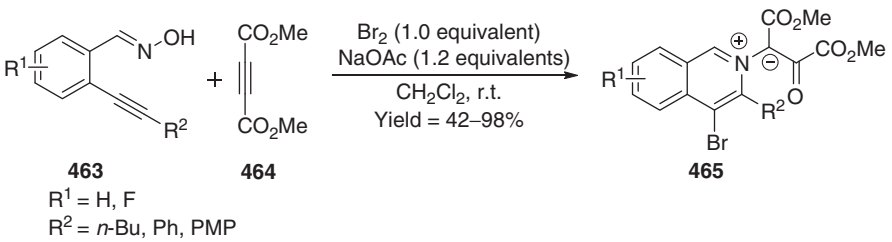
4.07.2.4.1 Cyclization involving alkenes

The Taguchi group developed a fluorolactonization of 4-alkenoic acid derivatives containing an aryl substituent at the 4- or 5-position with *N*-fluoropentachloropyridinium triflate, which proceeds smoothly in a regioselective manner with little or even no diastereoselectivity (Scheme 131).[141]

The Serguchev group realized the selective fluorolactonization of *cis*-5-norbornene-2,3-*endo*-dicarboxylic acid or its monomethyl and dimethyl esters with F-TEDA-BF_4 or XeF_2 (Scheme 132).[142] The reactions of 5-norbornene-*endo*-2-carboxylic acid or



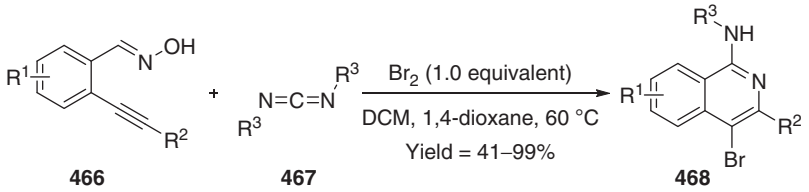
Scheme 121



Scheme 122

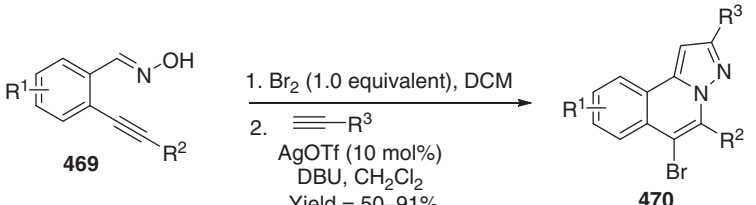
its methyl ester with F-TEDA-BF_4 or XeF_2 proceed unselectively with the formation of products of lactonization, addition, and rearrangements.

In 2003, Gouverneur and coworkers demonstrated that the electrophilic fluorodesilylation of allyl silanes combined with the use of enantiopure *N*-fluorocinchona alkaloids provided a highly efficient method for preparation of allylic fluorides with high *ee* values.[143] The $(DHQ)_2PYR$/Selectfluor combination fluorinated cyclic allylsilanes in MeCN to give five- and six-membered chiral allyl fluorides. The first asymmetric example was reported by Gouverneur and coworkers during a study of electrophilic

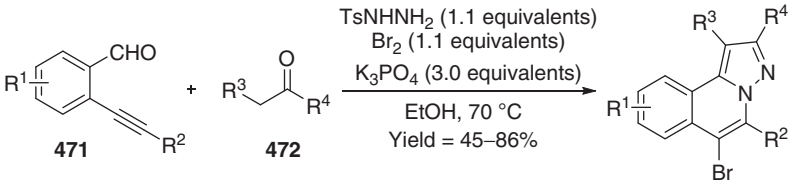


R^1 = H, F, Cl, Me, OMe
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, cyclopropyl

Scheme 123

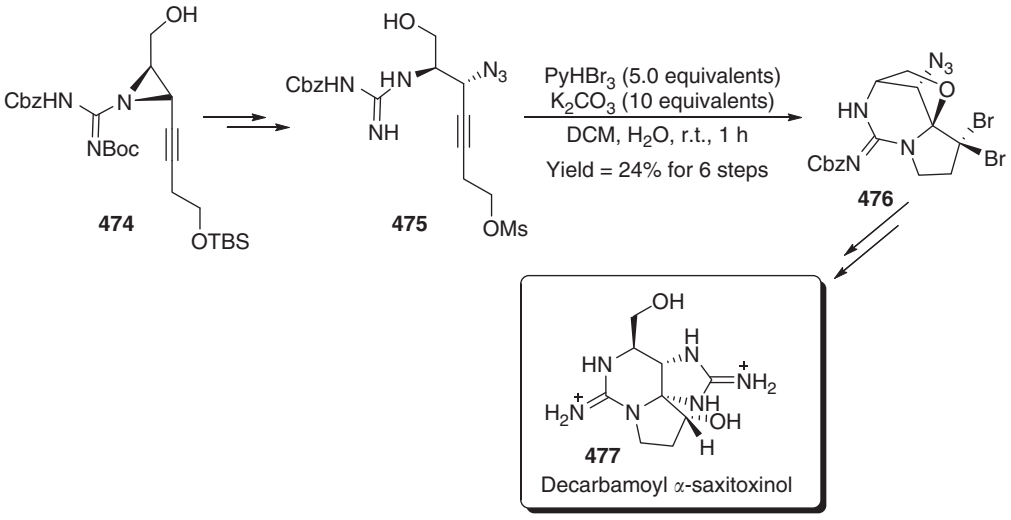


R^1 = H, F, OMe
R^2 = Ph, *n*-Bu
R^3 = Ph, *n*-Bu, PMP, CH_2OH; cyclopropyl

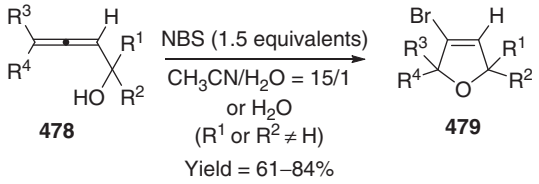


R^1 = H, F, Cl
R^2 = Ph,*n*-Bu,cyclopropyl
R^3 = H, Me, Et, $-(CH_2)_4-$
R^4 = H, Et

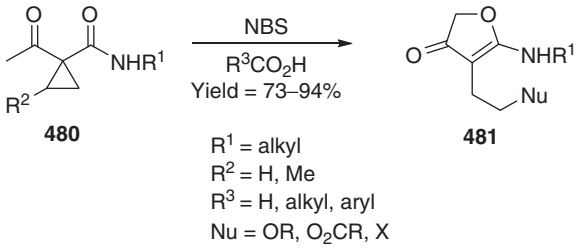
Scheme 124



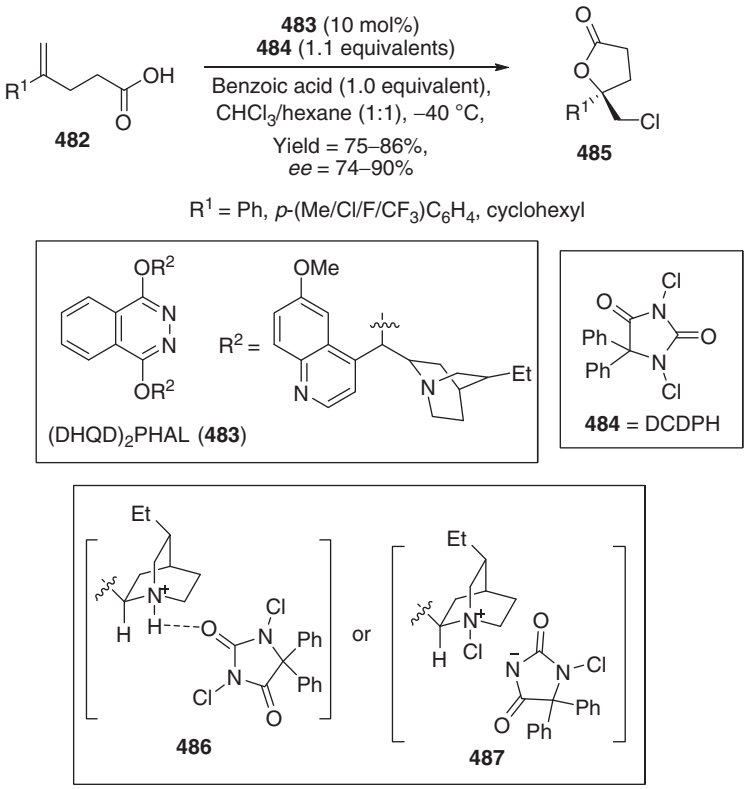
Scheme 125



Scheme 126



Scheme 127

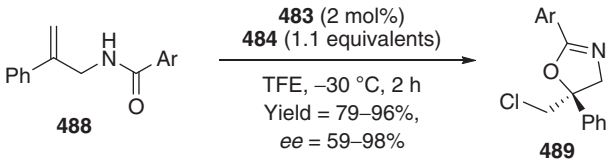


Scheme 128

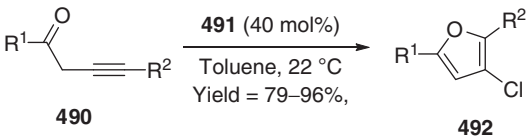
fluorocyclizations (Scheme 133).[144] The $(DHQ)_2PHAL$/Selectfluor combination could induce asymmetry in the cyclization of prochiral allyl silane **510** to produce **511** (70% yield, one diastereomer, 45% *ee*).

4.07.2.4.2 Cyclization of allenes

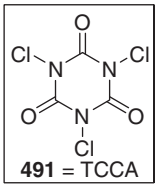
The fluorohydroxylation of 3-aryl-substituted-1,2-allenes with Selectfluor in aqueous MeCN at room temperature is reported by Ma's group.[145] This electrophilic reaction is highly regioselective with the more substituted and electron-rich C=C bond. However, the substrate scope is so far still very limited since the presence of the aryl group in allenes is important for the success of



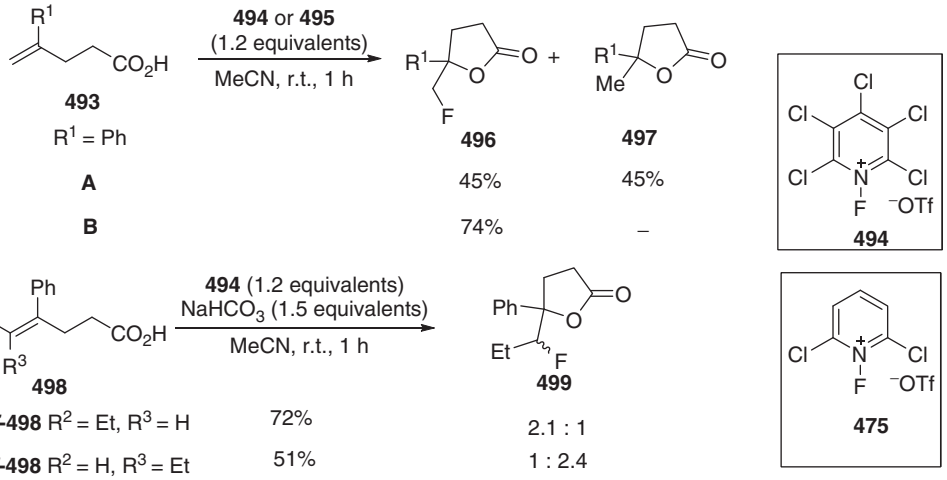
Scheme 129



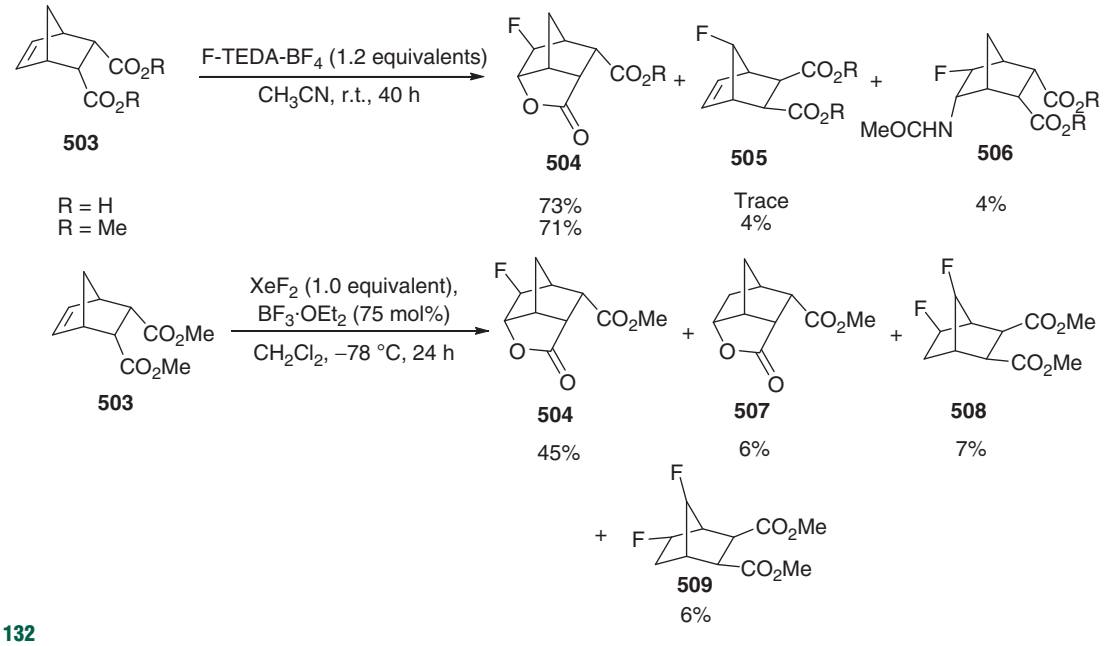
R^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4
R^2 = *p*-MeC_6H_4, *c*-C_6H_6, *p*-(*t*-Bu)C_6H_4



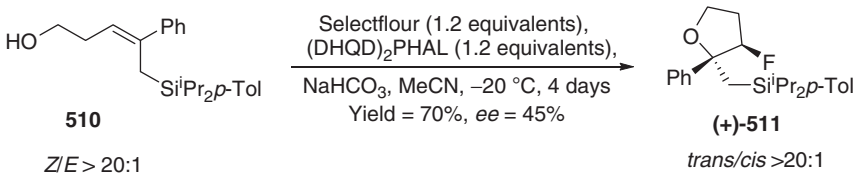
Scheme 130



Scheme 131

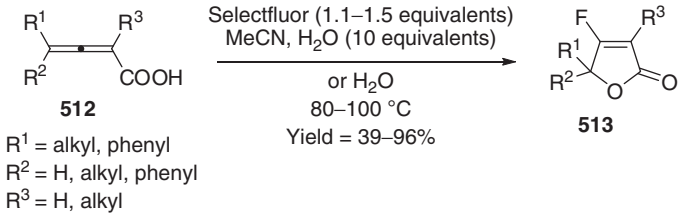


Scheme 132

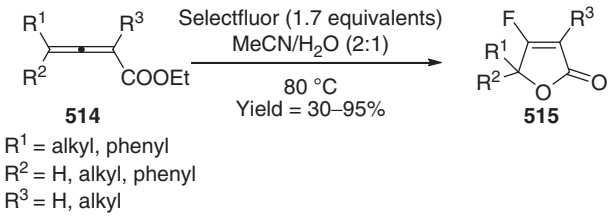


Scheme 133

this transformation. With Selectfluor as the electrophile, 2,3-allenoic acids may also be cyclized to afford *β*-fluorobutenolides (Scheme 134).[146] 2,3-Allenoates, which are more readily available, are developed to prepare 4-fluoro-2(5*H*)-furanones (Scheme 135).[147] If 3.0 equivalents Selectfluor and 0.5 equivalent H_2O were used, 3-fluoro-4-oxo-2(*E*)-alkenoates could be obtained.[147]



Scheme 134



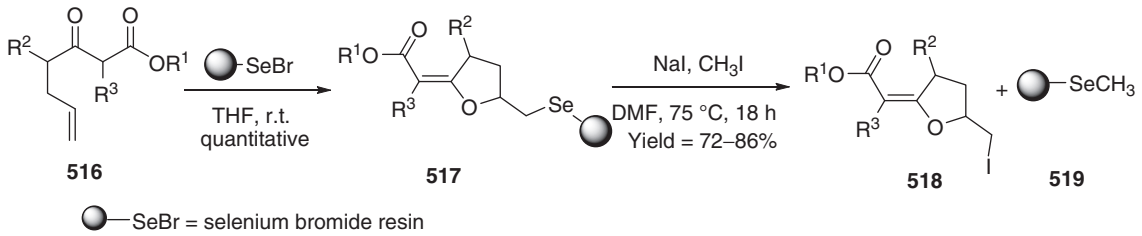
Scheme 135

In this part, iodocyclization, bromocyclization, chlorocyclization, and fluorocyclization are summarized. Many wonderful methodologies have been used as key steps in the synthesis of natural products. Besides halocyclization, selenocyclization, sulfenylcyclization, and tellurocyclization are also traditional electrophilic cyclization, which will be discussed in the next section.

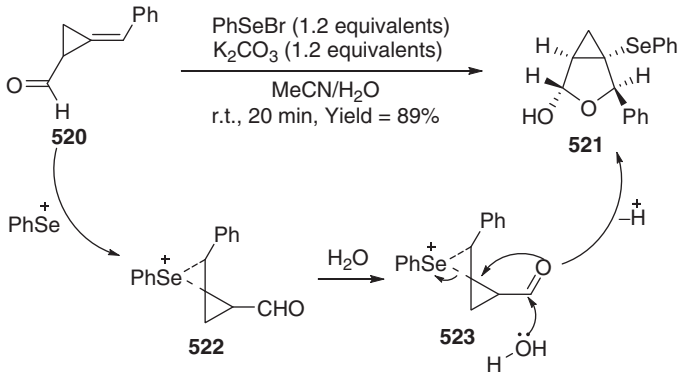
4.07.3 Sulfenylcyclization, Selenocyclization, and Tellurocyclization

4.07.3.1 Cyclization Involving Alkenes

Over the past more than 20 years, a large number of researches on intramolecular selenocyclization, sulfenylcyclization and tellurocyclization have been reported. In 2004, Huang and coworkers reported a selenium-induced intramolecular electrophilic cyclization for the synthesis of polysubstituted dihydrofurans and THFs, followed by selenoxide *syn*-elimination or novel nucleophilic substitution cleavage of selenium resin with good yields and purities (Scheme 136).[148] Then in 2009, the same group developed a new method for the preparation of 3-oxabicyclo[3.1.0]hexan-2-ols by the cyclization of (*E*)-2-(arylmethylene)-cyclopropylaldehyde mediated by different organoselenium reagents (Scheme 137).[149]



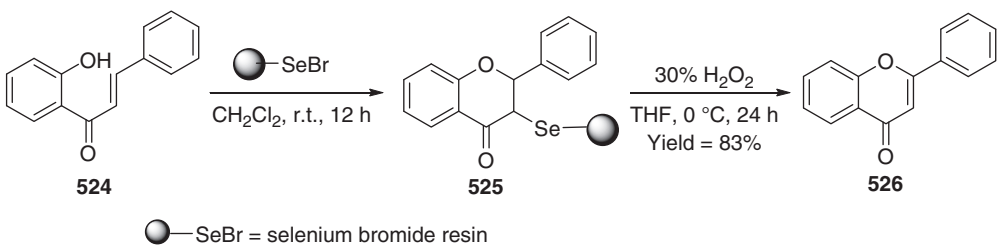
Scheme 136



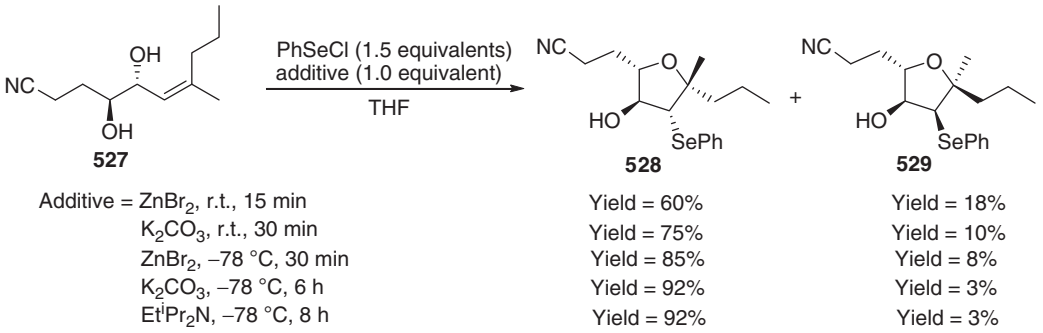
Scheme 137

A solid-phase synthetic method is developed for the preparation of flavonoids with good yields and purities (Scheme 138).[150]

The THF moiety of amphidinolides **528** and **529** is achieved in excellent yields by a cyclization of an *anti* dihydroxy (allylic and homoallylic), unprecedented trisubstituted-alkene substrate (**527**), followed by deselenylation. The highly selective selenocyclization reaction is the key step in this transformation (Scheme 139).[151]

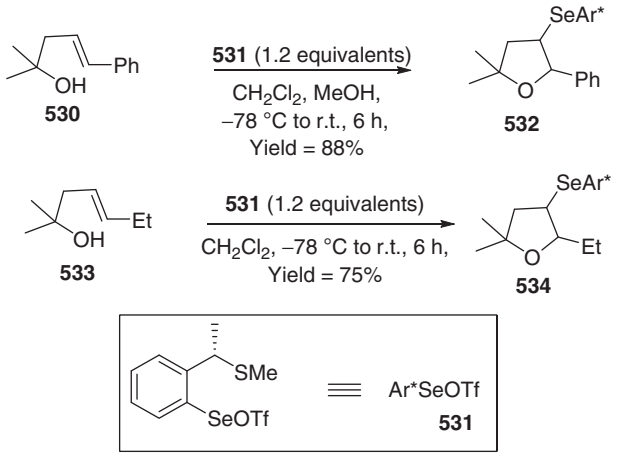


Scheme 138



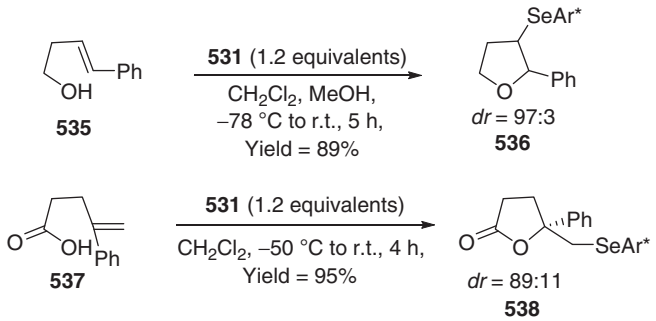
Scheme 139

Some chiral electrophilic selenium reagents have been developed for reagent-controlled asymmetric synthesis, such as chiral aryl and terpene-derived selenides. The selenoetherification of compound **530** gave product **532** in 88% yield with a diastereomeric ratio of 93:7, and compound **533** converted into product **534** in 75% yield with a diastereomeric ratio of 89:11. In both cases, Ar*SeOTf **531** should be prepared at $-78\ ^{\circ}C$ and then the mixture should be allowed to reach room temperature and stirred for another 6 h (Scheme 140).[152]



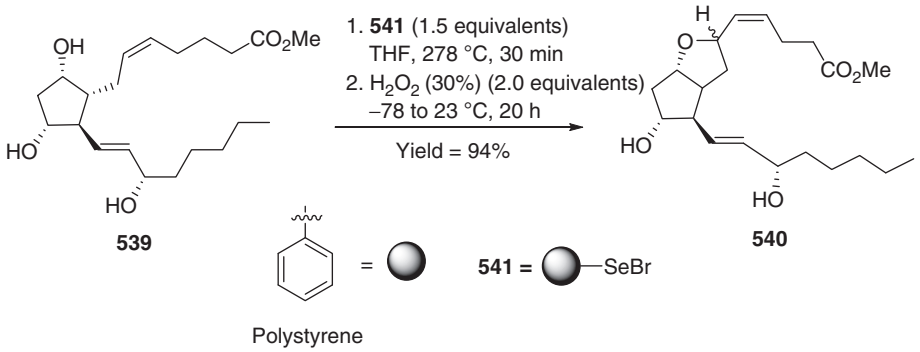
Scheme 140

Chiral sulfur-containing selenides have been used successfully in promoting the asymmetric electrophilic functionalizations affording furan derivatives. The diastereoselectivities of these reactions are proved to be good (Scheme 141).[153]



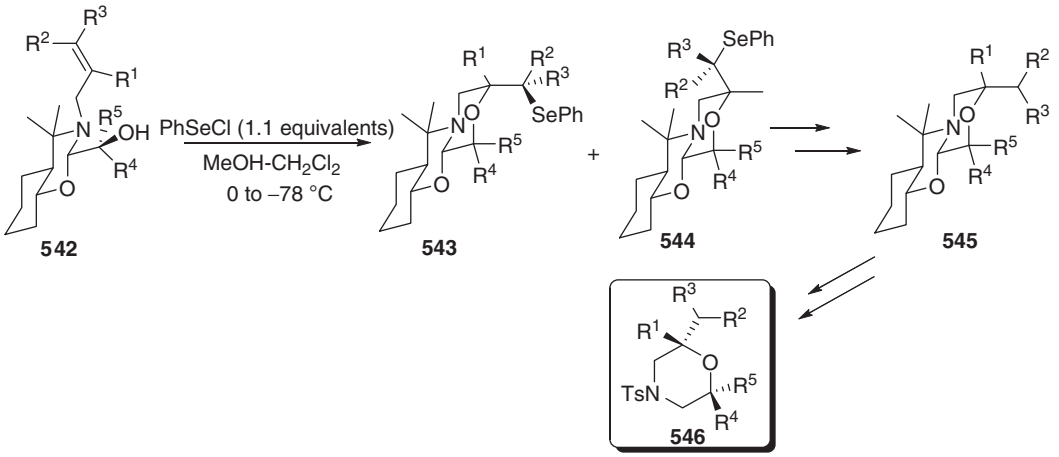
Scheme 141

The polymer-bound selenium bromide **541** has been applied for the two-step transformation of PGF2α methyl ester **539** to the PGI_2 analogs **540** (94% yield, approximately 2:1 ratio of C-6 epimer). This method is used successfully in preparing a series of polymer-bound selenium reagents/linkers (Scheme 142).[154]



Scheme 142

Diastereoselective synthesis of enantiopure morpholines by electrophilic selenium-induced 6-*exo* cyclizations on chiral 3-allyl-2-hydroxymethylperhydro-1,3-benzoxazine derivatives is developed by Pedrosa and coworkers (Scheme 143).[155]



Scheme 143

In 2000, Nicolaou and coworkers reported a method for the solid-phase construction of 2,2-dimethylbenzopyrans employing a selenium-based linking strategy wherein the loading step constitutes a key ring-forming reaction. Once the benzopyrans form, they can be elaborated to a variety of natural products and analogs thereof. Finally, it is easy to cleavage the resin and functionalize in high purity and efficiency (Scheme 144).[156] The hepta-acetate of the natural product macropylloside D is synthesized. Using the same strategy, some examples of potential pharmaceutical candidates incorporating the 2,2-dimethylbenzopyran moiety are synthesized.[157]

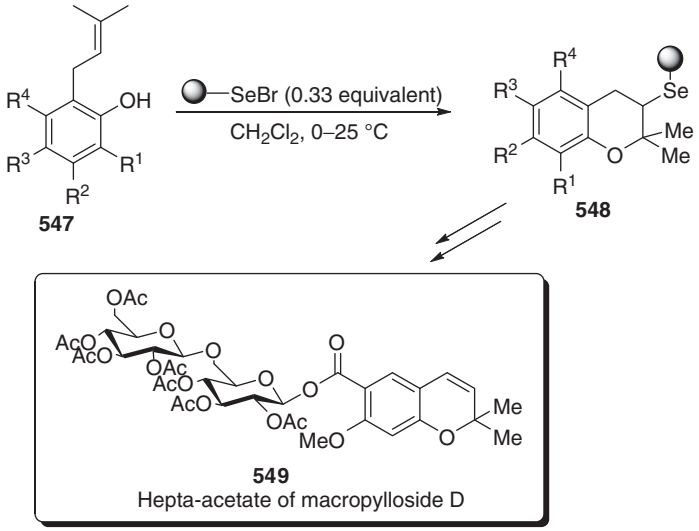
In the total synthesis of phytuberin, an unprecedented 4-*exo* selenocyclization of a homoallylic alcohol affording oxetane derivatives is developed (Scheme 145).[158]

In the total synthesis of leucascandrolide A, Carreira and coworkers constructed a 2,6-*trans*-substituted tetrahydropyran by selenium-mediated intramolecular cyclization in a high yield (Scheme 146).[159] It is the first example of a stereoselective synthesis of a 2,6-trans-disubstituted tetrahydropyran mediated by a bulky Se-electrophile.

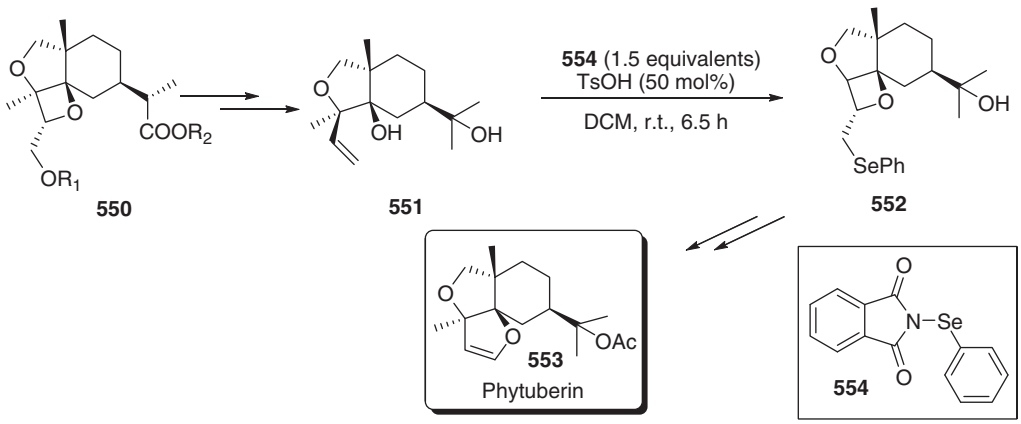
In the field of Se-induced cyclization, the use of catalytic selenium electrophiles is reported.[160] Butenoic acids **558** are exposed to 5 mol% diphenyl diselenide and stoichiometric [bis(trifluoroacetoxy)iodo]benzene in acetonitrile affording butenolides **559** in high yields (Scheme 147).[160] When a catalytic amount of Lewis base is used, significant rate enhancement is observed in the typical selenolactonizatin reactions (Scheme 148).[160b]

The asymmetric synthesis of cyclic ethers by selenocyclizations has attracted broad interest in recent years, especially in the total synthesis of natural products.[161] In the total synthesis of salinosporamide A, Danishefsky and coworkers used a selenocyclization with an *in situ* formed nucleophilic hydroxyl group as a key step (Scheme 149).[162]

Kim and coworkers accomplished an asymmetric total synthesis of trilobacin via organoselenium-mediated oxonium ion formation/SiO_2-promoted fragmentation (Scheme 150).[163]



Scheme 144



Scheme 145

Very recently, Kim and coworkers completed the first total syntheses of both enantiomers of the marine natural product elatenyne as well as its double-bond isomer (*E*)-elatenyne (Scheme 151).[164] Selenocyclization was used for the construction of two furan rings. The dibrominated 2,2′-bifuranyl **582** was obtained in 70% yield through exposure the substrate **577** to PhSeBr, activated silica gel and potassium carbonate.

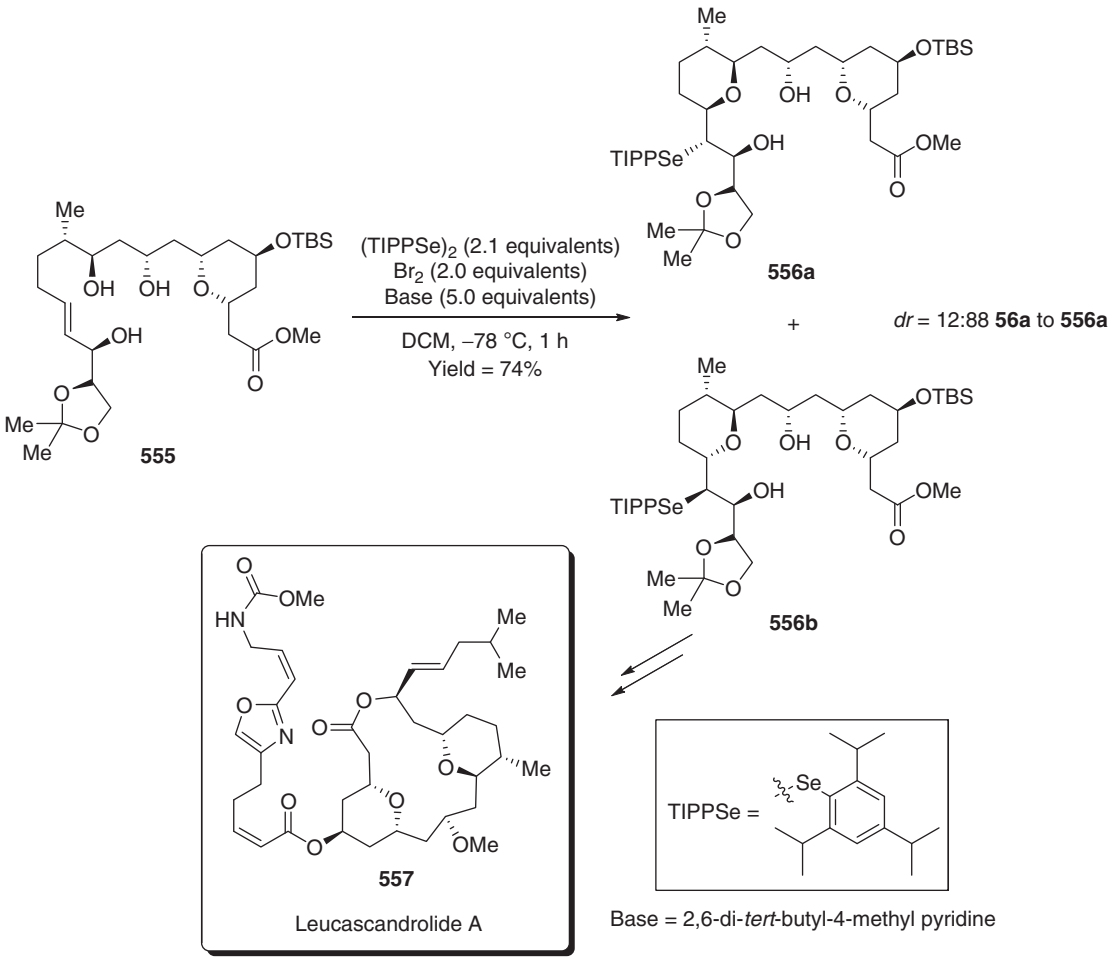
The reaction of (*E*)-*N*-benzyl-1-(2-benzylidenecyclopropyl)methanamine with PhSeBr stereoselectively gives ring-closure product 1-phenylselenenyl-2-aryl-3-azabicyclo[3.1.0]-hexane in good yields at room temperature (Scheme 152).[77]

An application of electrophilic selenium reagent *N*-PSP to promote a cyclization with an internal nitrogen nucleophile is reported by Yao and coworkers in the total synthesis of chloptosin. The diastereoselective selenocyclization and oxidative deselenation successfully serve as the key steps in the effective bidirectional synthesis of the core amino acid in this work (Scheme 153).[165]

Ley and coworkers developed an interesting application of the selenocyclization of amines to construct the important 3a-hydroxypyrrole[2,3-*b*]indole core. This method has been applied successfully in the total synthesis of okaramine C (Scheme 154).[166]

An improved procedure for the selenium-mediated cyclization of alkenyl-substituted *β*-dicarbonyls to form a variety of bicyclo[3.3.1]nonan-9-ones has been developed for the synthesis of bicyclic natural products from the Guttiferae classification by the Nicolaou group (Scheme 155).[167] The reaction proceeds successfully both in solution and on solid support, and the behaviors is closely correlated almost in the all cases.

Wirth and coworkers reported a new cyclization of *β*-keto ester-substituted stilbene derivative **605** using PhSeCl in the presence of Lewis acid $FeCl_3$ (Scheme 156).[168]



Scheme 146

Shaw et al. developed a new methodology for the synthesis of substituted tetrahydroquinolines with $Sc(OTf)_3$ as an effective and practical precatalyst. Two rings, three bonds, and three stereogenic centers with excellent stereo- and regiocontrol were constructed in a single step (Scheme 157).[169]

4.07.3.2 Cyclization Involving Alkynes

Electrophilic cyclization of 1-(1-alkynyl)-cyclopropyl ketones affords highly substituted furans in good to excellent yields under mild conditions (Scheme 158).[59]

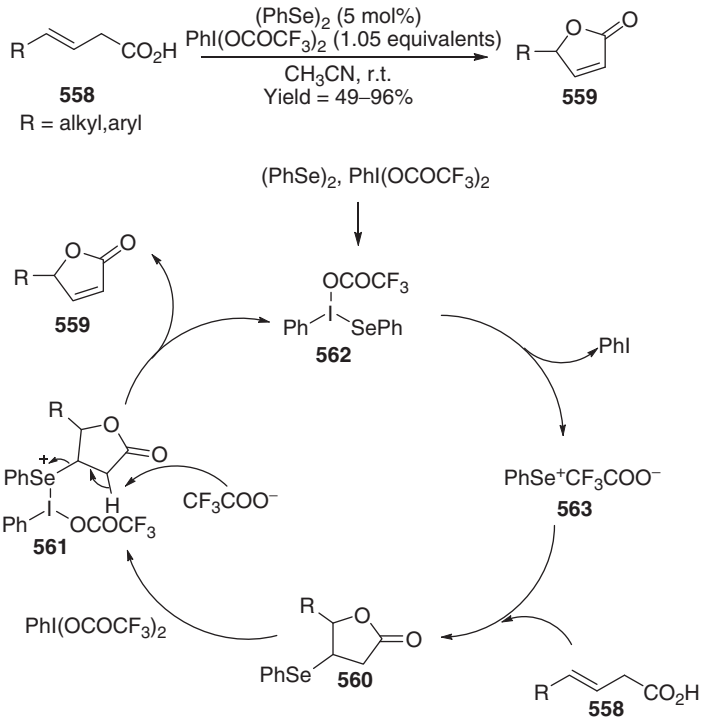
The methodologies of selenocyclization and sulfenylcyclization of alkyne have also been widely investigated by Larock and coworkers, and some of the typical examples are shown in Schemes 159.[101,170]

4.07.3.3 Cyclization Involving Allenes

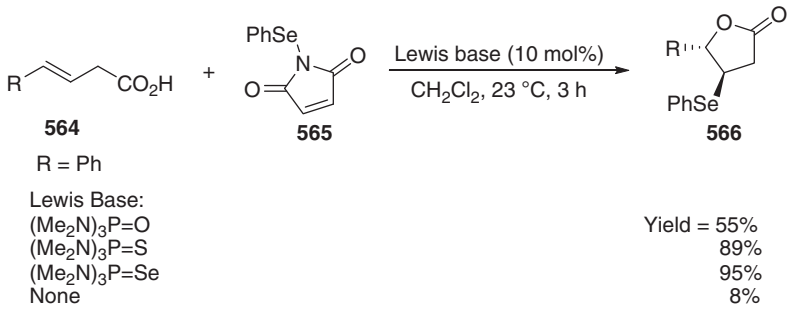
Ma and coworkers developed a facile and effective synthesis of β-organoselenium-substituted butenolides from 2,3-allenoates and PhSeCl in water (Scheme 160).[171]

A convenient and highly efficient method for the preparation of β-organotellurobutenolides via ArTeCl-induced electrophilic tellurolactonization of α-allenoic acids is developed by Huang et al. (Scheme 161).[172]

The cyclization of allenylcarbinol **573** with PhSeCl in DCM afforded a single selenophenyl dihydrofuran **574** in 66% yield along with 17% of the presumed (*E*)-allylic alcohol **575** (one isomer). Both $AgNO_3$ and NBS could promote the cyclization in good yields with high stereoselectivity (Scheme 162).[173]



Scheme 147



Scheme 148

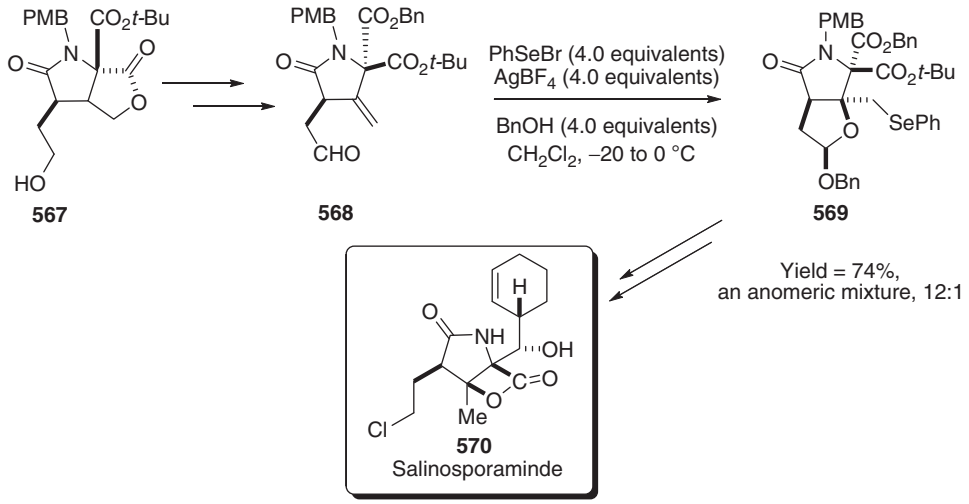
4.07.4 Hg-, Ag-, Au-, and Pt-Catalyzed Electrophilic Cyclization

Besides the traditional electrophiles mentioned in Figure 3(a)), transition metal, as a π-acid catalyst, could also activate C–C multiple bond via coordination, which is fundamental to organometallic chemistry (Figure 3(b)). The M^+ could play the same role as E^+ to induce the cyclization. The Wacker process for the conversion of ethylene into acetaldehyde is a classic example of an efficient electronphilic-type cyclization that begins with the coordination of ethylene to Pd^{II}, which activates the ethylene moiety toward nucleophilic attack by water.[174] Till now, Pd, Pt, Hg, Au, and Ag have been employed to induce the cyclizations. Besides palladium, which has developed into a diversity and complicated system, mercury-, gold-, silver-, and platinum-catalyzed electrophilic cyclization used in the synthetic applications will be discussed in the following section.

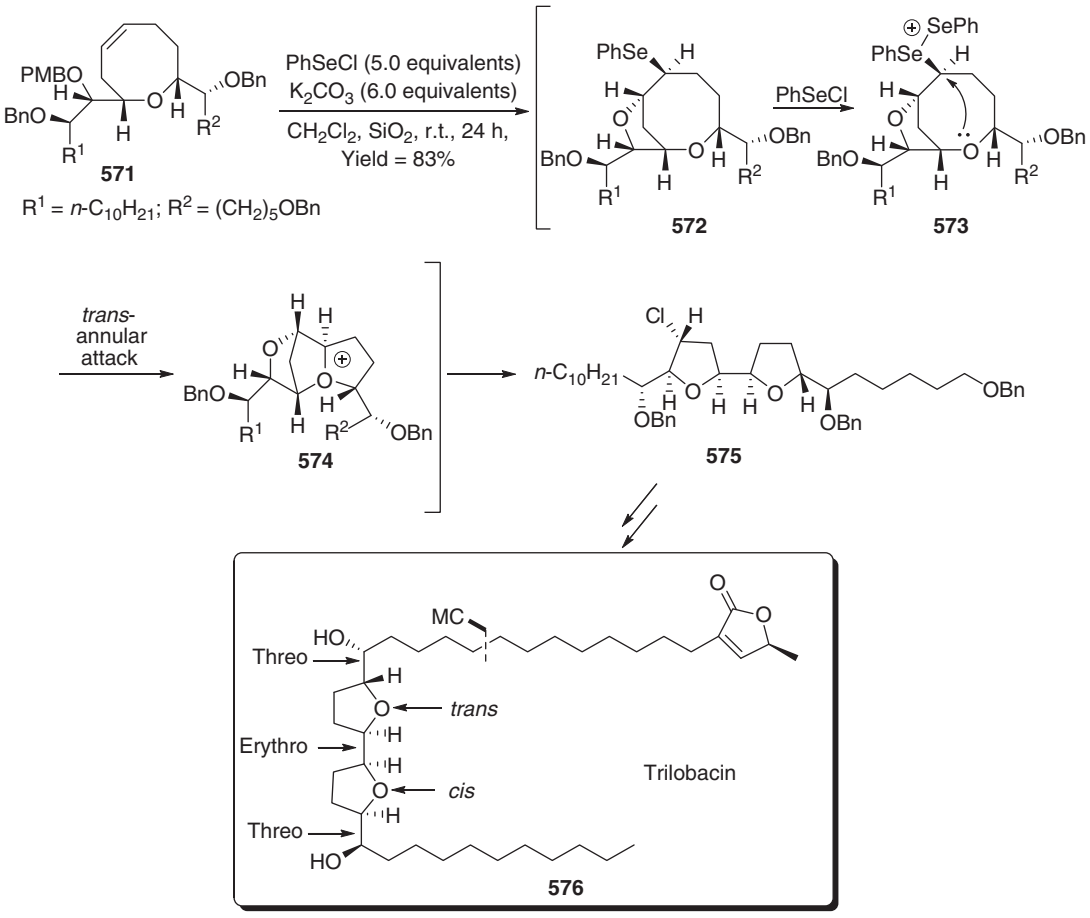
4.07.4.1 Mercury-Catalyzed Cyclization

Cyclization promoted by mercury salts is of certain synthetic interest, owing to the easy replacement of the mercury-containing residue by an oxygen or nitrogen nucleophiles. There have been numerous synthetic applications of the reaction, and some reviews have been published.[175]

A 6′(*R*)-hydroxymethyl derivative of the locked nucleic acid (LNA)-thymidine monomer has been synthesized by a stereoselective mercury cyclization, and there has been subsequent use of TEMPO as a radical scavenger. It is finally reduced by zinc and HOAc to give compound **638** in an yield of 83% (Scheme 163).[176]



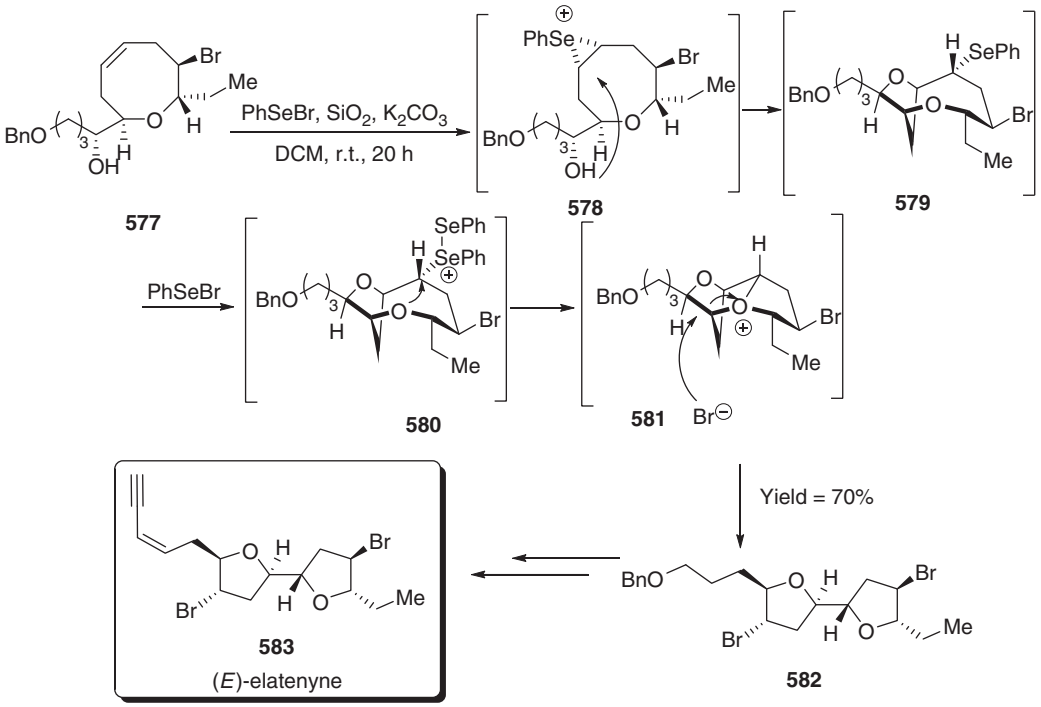
Scheme 149



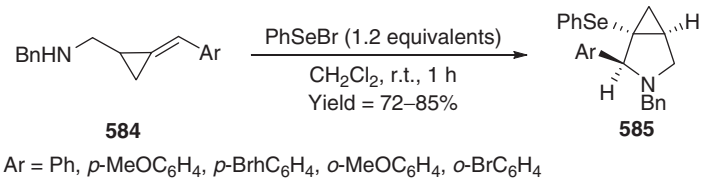
Scheme 150

Stereocontrolled routes to 2,3-dihydro-4*H*-pyran-4-ones by the Hg(II)-catalyzed rearrangement of 1-alkynyl-2,3-epoxy alcohols in acidic media has been developed by Marson and coworkers (Scheme 164).[177]

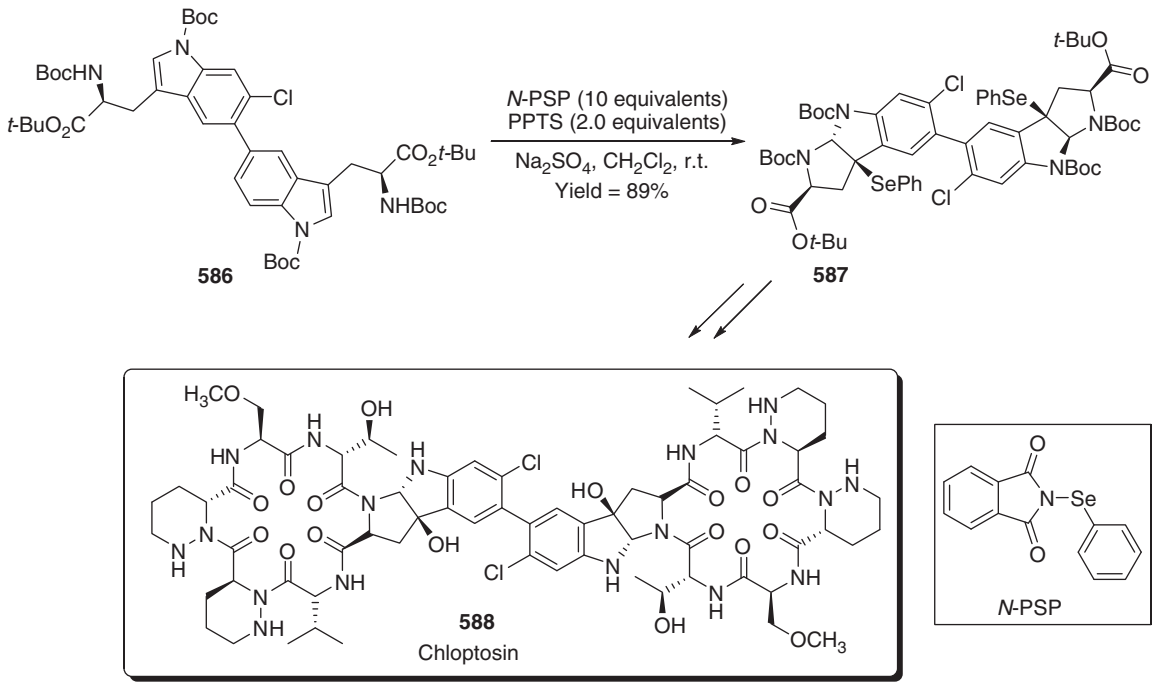
Deslongchamps and coworkers demonstrated that the Hg(II) catalysts are highly efficient and economical ($HgCl_2$) by utilizing a simple experimental procedure for the synthesis of various saturated and unsaturated spiroketals and furans (Scheme 165).[178]



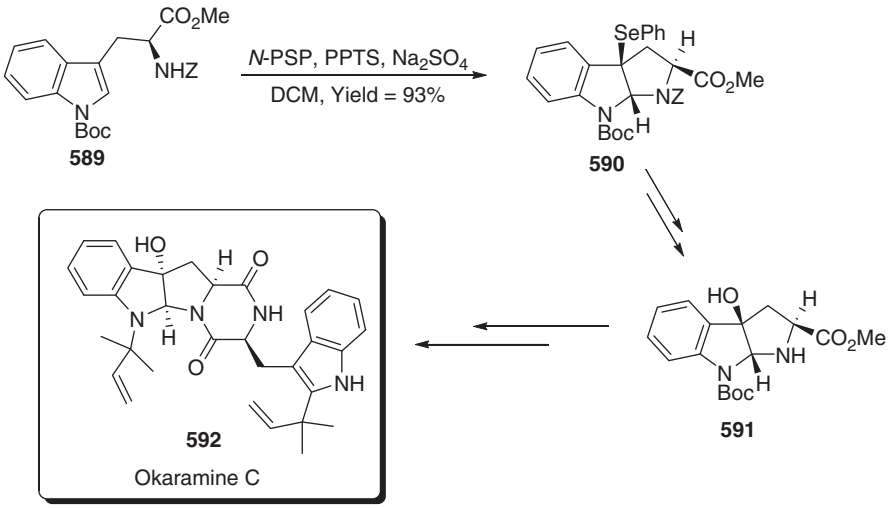
Scheme 151



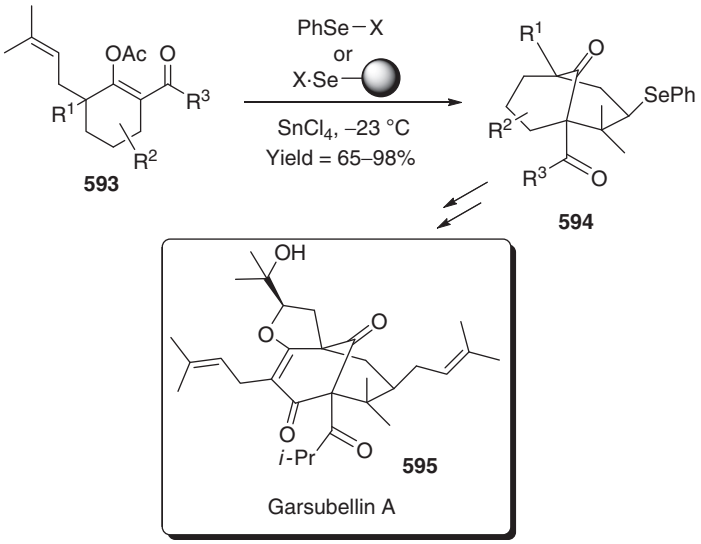
Scheme 152



Scheme 153



Scheme 154



Scheme 155

Kim and coworkers developed a facile method for the synthesis of 3-(alkylamino)-5-arylthiophenes having acyl-, aroyl-, or ethoxycarbonyl substituents at C-2 using thioaroylketene *S,N*-acetals, mercury(II) acetate, and active methylene compounds (Scheme 166).[179]

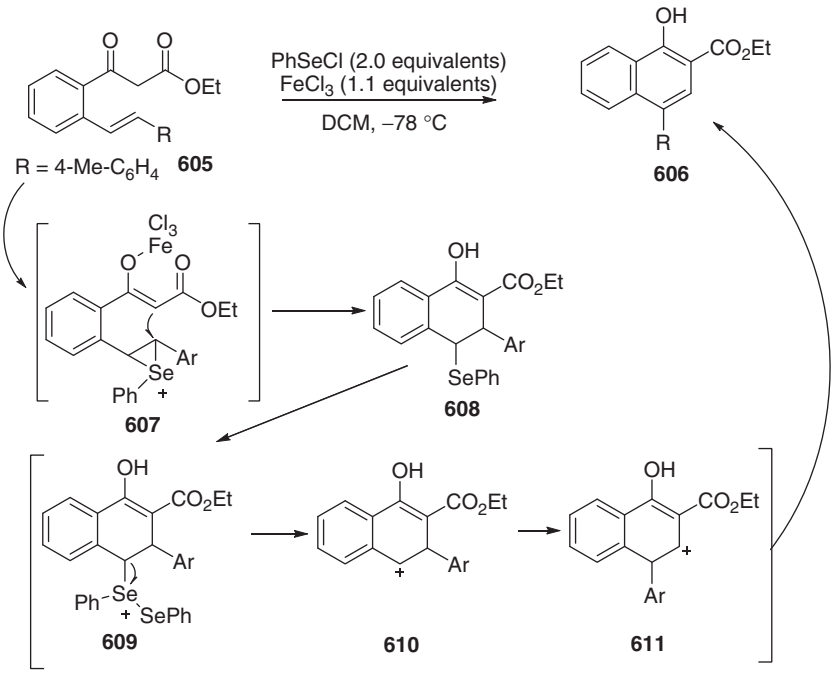
Bhattacharjya and coworkers describe Hg(II)-mediated reaction of *O*-propargyl glycolaldehyde dithioacetals and an expedient general route to 6*H*-pyran-3-ones (Scheme 167).[180]

An efficient method for the construction of dihydroquinoline derivatives possessing a quaternary carbon center is developed by an application of $Hg(OTf)_2$-catalyzed vinylogous semi-pinacol-type rearrangement. The reaction was found to be specifically catalyzed by mercury salt via a bicyclic aminal (Scheme 168).[181]

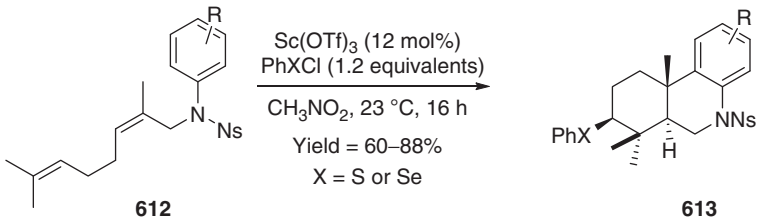
$Hg(OTf)_2$-catalyzed arylene cyclization was achieved with highly efficient catalytic turnover (up to 200 times) by Nishizawa's group. The reaction takes place via protonation of allylic hydroxyl group by *in situ* formed TfOH of an organomercuric intermediate to generate a cationic species (Scheme 169).[182]

In 2007, Nishizawa and coworkers report that a 10:1 mixed reagent of $Hg(OAc)_2$ and $Sc(OTf)_3$ showed remarkable catalytic activity for the Friedel-Crafts-type cycloisomerization of 2-(4-pentynyl)furan (Scheme 170).[183] The actual reacting species is presumed to be Hg(OAc)(OTf), which is efficiently generated *in situ* by mixing the two reagents.

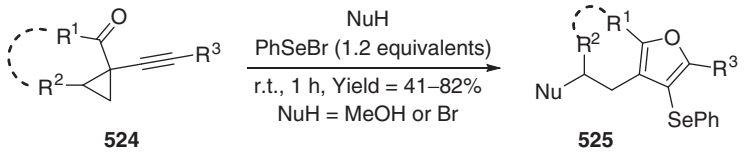
Cycloisomerizations of allenynes to allenenes have been investigated in the presence of $[Hg(OTf)_2]$ in MeCN. It is quite effective for constructing terminal 1,6-allenynes (Scheme 171).[184]



Scheme 156



Scheme 157



Scheme 158

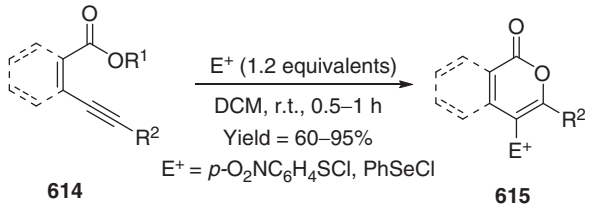
Yamamoto and coworkers described the preparation of solid-supported silaphenylmercuric triflate. Several examples of silaphenylmercuric triflate-catalyzed reactions such as indole synthesis, furanoyne cyclization, arylyne cyclization, and tandem carbocyclizations have been developed (Scheme 172).[185]

An efficient synthesis of hippuristanol and some of the close analogs has been achieved from readily available hecogenin acetate through an unprecedented $Hg(OTf)_2$-catalyzed cascade spiroketalization as the most convenient strategy (Scheme 173).[186]

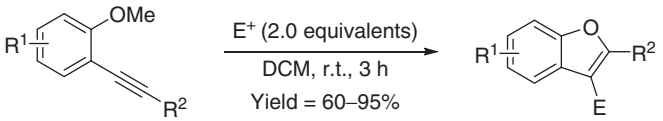
In the total synthesis of (±)-thallusin, homofarnesyl acetate performs cyclization using $Hg(OTf)_2{\cdot}PhNMe_2$-induced olefin cyclization in an excellent yield (Scheme 174).[187]

4.07.4.2 Silver-Catalyzed Cyclization

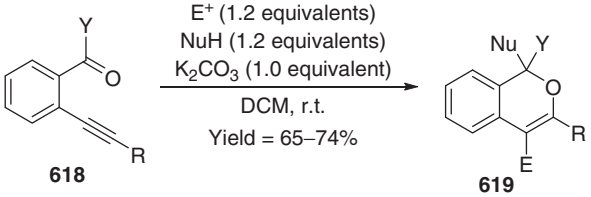
Mercuric salts were used for more than 70 years, leading to many applications to intermolecular and intramolecular additions of various nucleophiles to unsaturated C–C bonds. Because of the high toxicity of mercuric salts, several other catalysts are



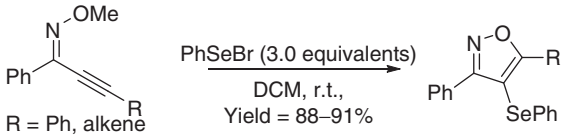
614 **615** (1)



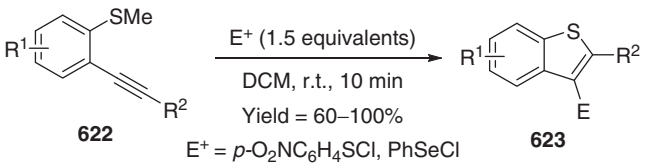
616 **617** (2)



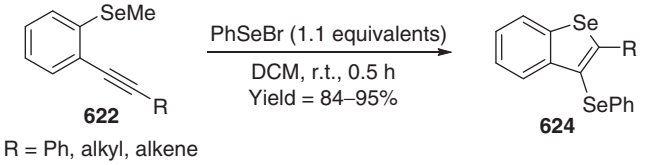
618 **619** (3)



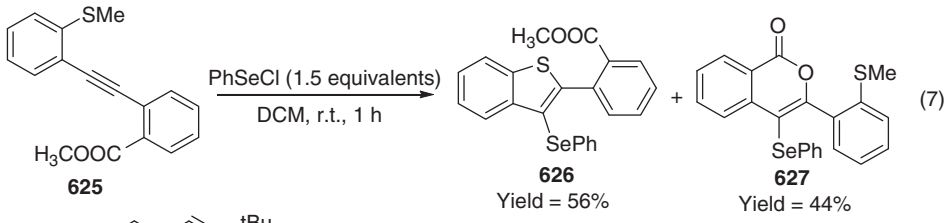
620 **621** (4)



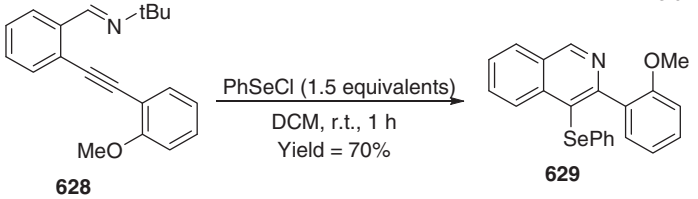
622 **623** (5)



622 **624** (6)

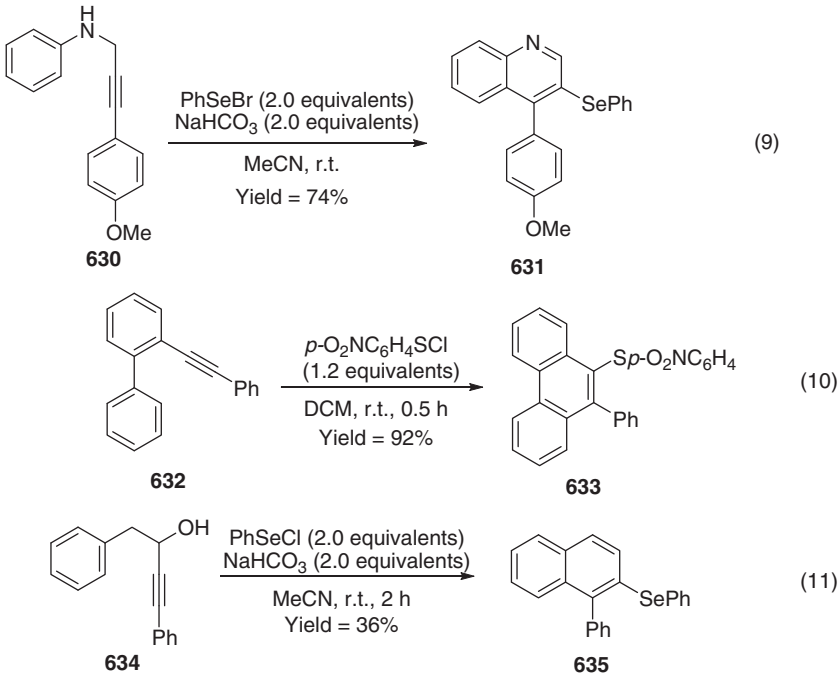


625 **626** **627** (7)

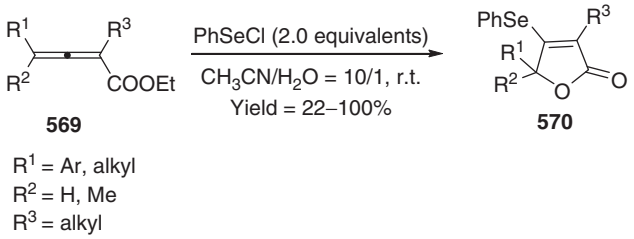


628 **629** (8)

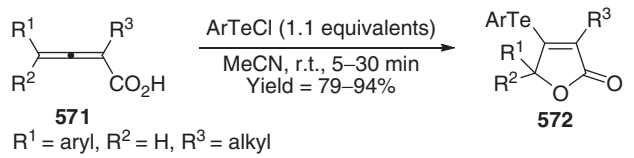
Scheme 159



Scheme 159 (continued)



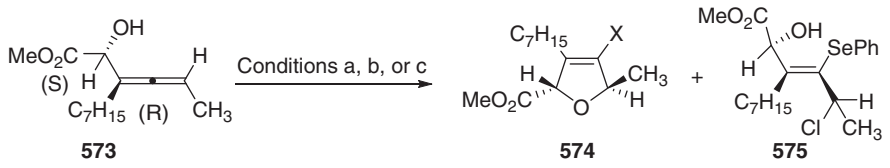
Scheme 160



Scheme 161

developed. The silver salts are proved to be the most efficient catalysts. Cyclization reactions exhibit high interest in organic synthesis, especially when starting from alkynes or allenes since the cyclization products retain an olefin, which can be further manipulated, opening a wide variety and diversity of applications. Moreover, the nature of the cyclization products can be varied by changing silver counterion and/or reaction conditions, and many intramolecular heterocyclizations proceed with high diastereoselectivities. There have been many reviews summarizing this kind of reaction.[188]

Silver-induced cyclization reactions have been used in the total synthesis widely used in recent years. In the total synthesis of (+)-pamamycin-607, silver-assisted iodoetherification is proved to be a key step for its high enantioselectivity. The tetrahydrofurans rings with complete *cis*-stereoselectivity are formed from silylated hydroxalkene and iodine in the presence of silver carbonate (Scheme 175).[189]



573 **574** **575**

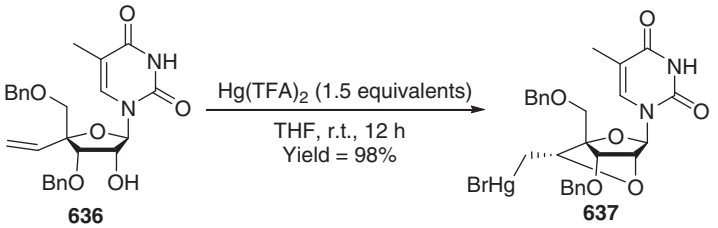
a. PhSeCl, CH_2Cl_2, r.t, 5 min; X = SePh — 66%
b. $AgNO_3$, Ca_2CO_3, MeOH-H_2O, r.t., 48 h; X = H — 84% — 17%
c. NBS, CH_2Cl_2, r.t., 48 h; X = Br — 66%

Scheme 162

E^+ = Halogen, S, Se, Te **(a)**

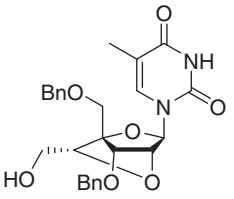
M^+ = Transition Metal **(b)**

Figure 3 Electronphilic activation.



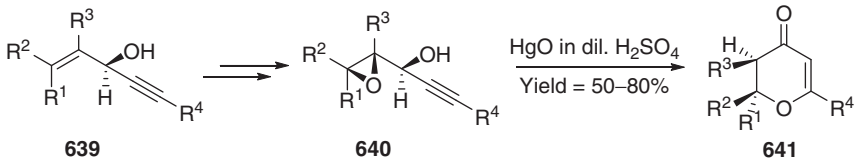
636 **637**

1. TEMPO, $NaBH_4$, 77%
2. Zn, HOAc, 83%



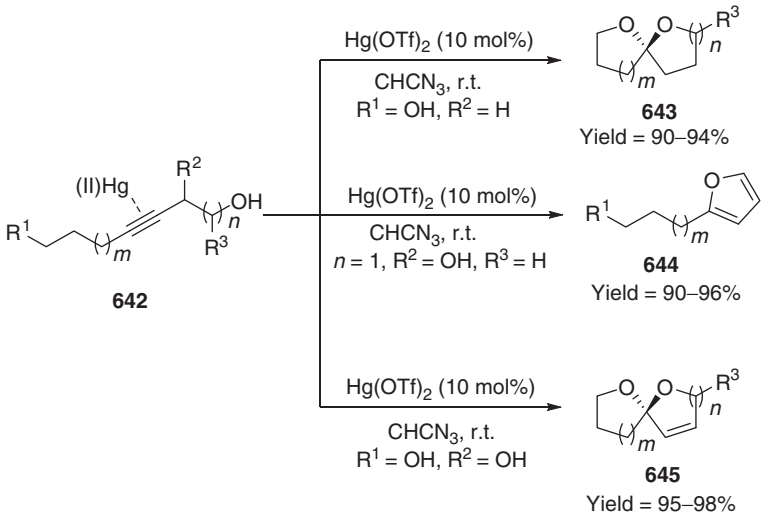
638

Scheme 163

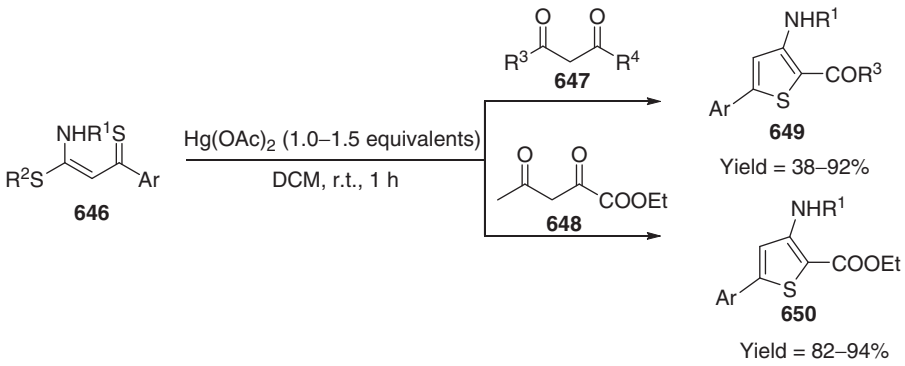


639 **640** **641**

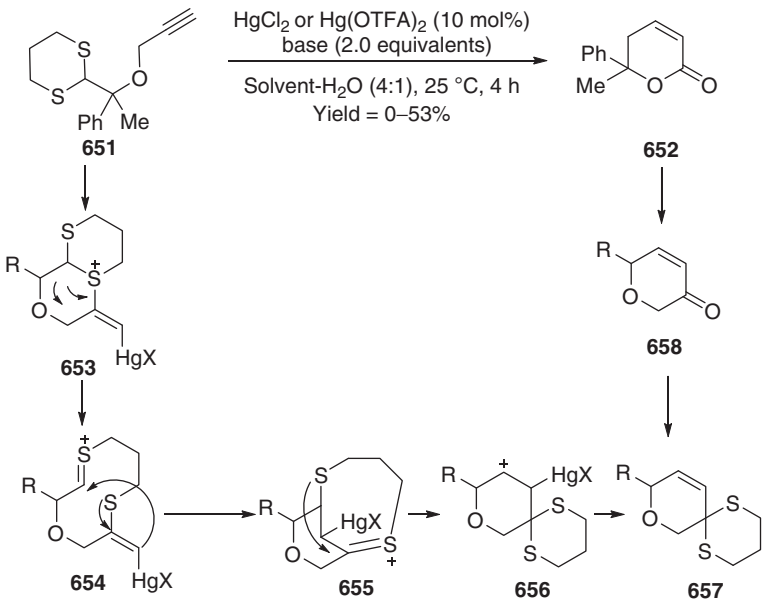
Scheme 164



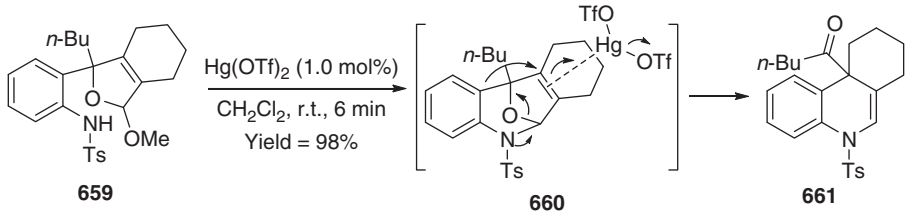
Scheme 165



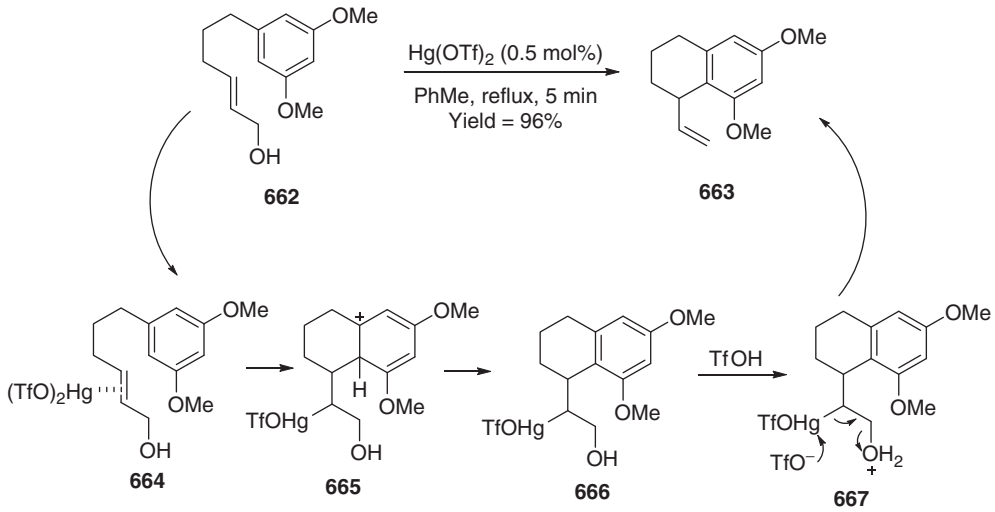
Scheme 166



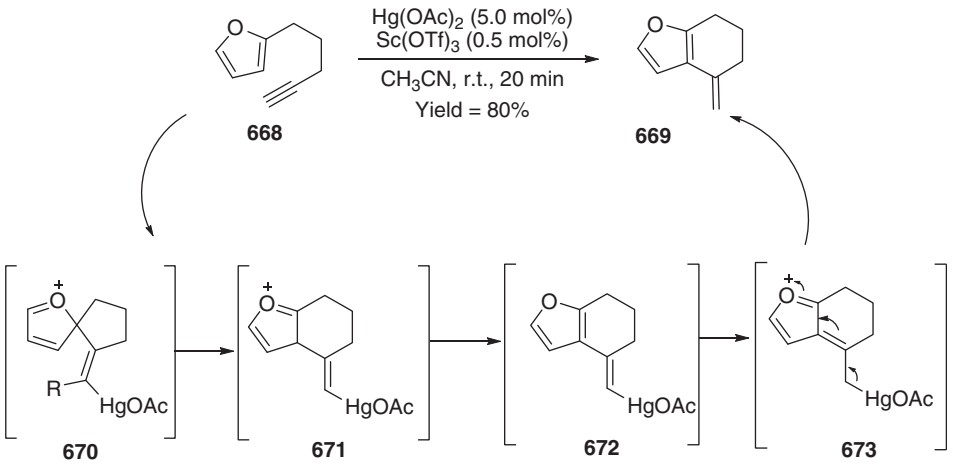
Scheme 167



Scheme 168



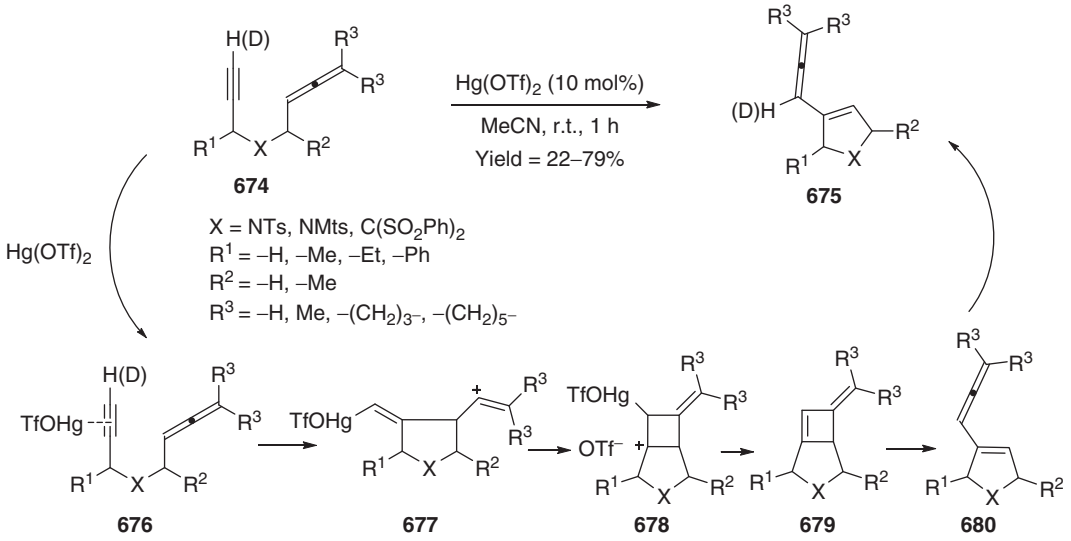
Scheme 169



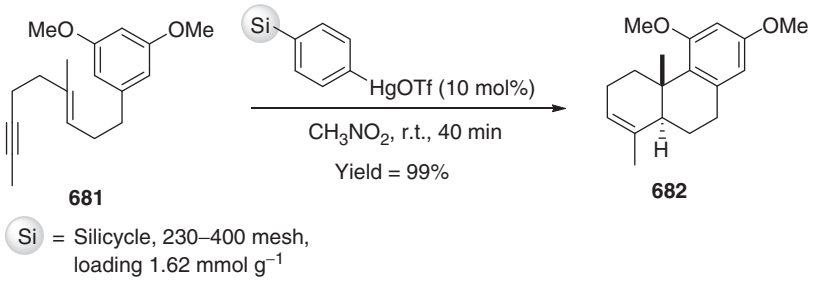
Scheme 170

The Ag^+-mediated cyclization of allenic alcohols has been applied to the synthesis of various natural products and analogs. Verrucosidin, citreoviridin, and their metabolite citreal have been prepared via an Ag^+-promoted stereoselective cyclization of a dihydroxyallene (Scheme 176).[190]

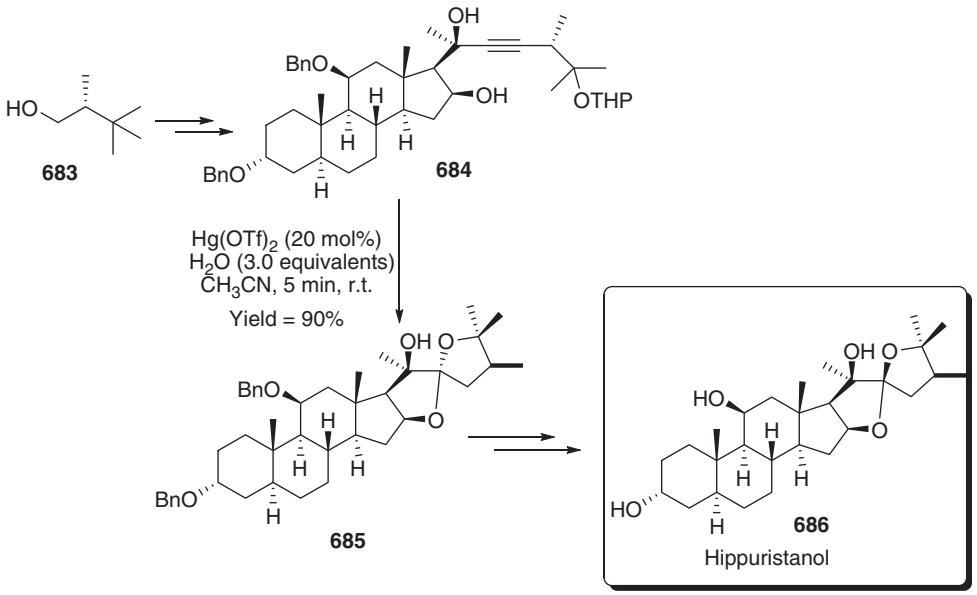
Standaert and coworkers reported a concise and modular synthesis from the Garner aldehyde and proceeding in seven steps to furanomycin. The key steps include a stereoselective acetylide addition and the Ag^+-mediated cyclization of an α-allenic alcohol to construct the *trans*-2,5-dihydrofuran (Scheme 177).[191]



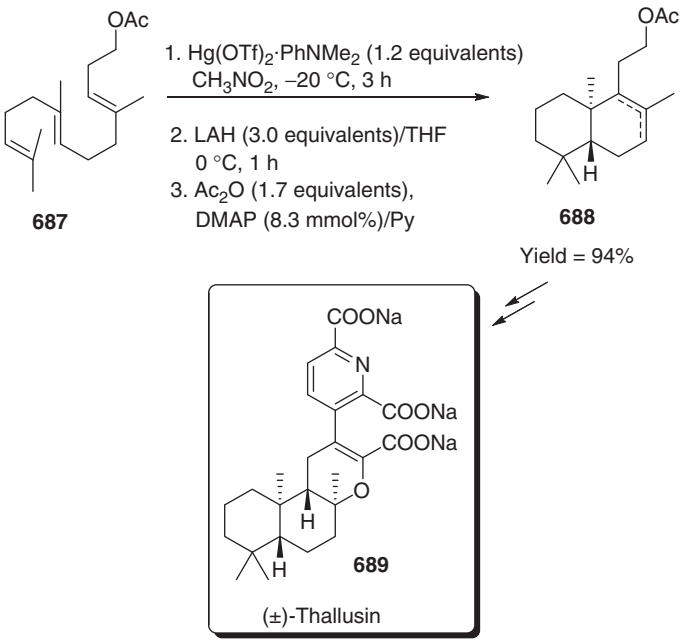
Scheme 171



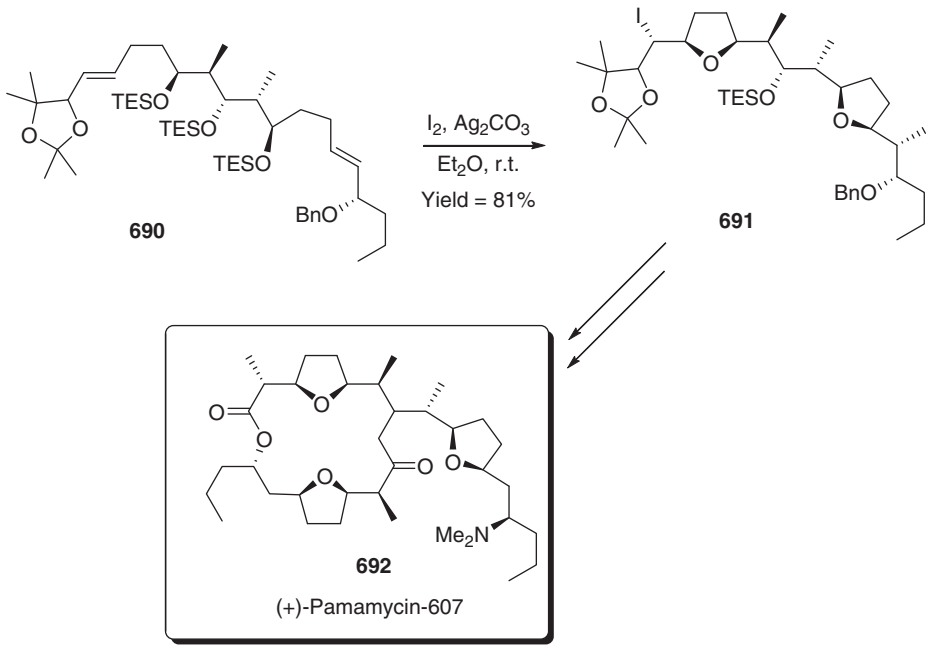
Scheme 172



Scheme 173



Scheme 174

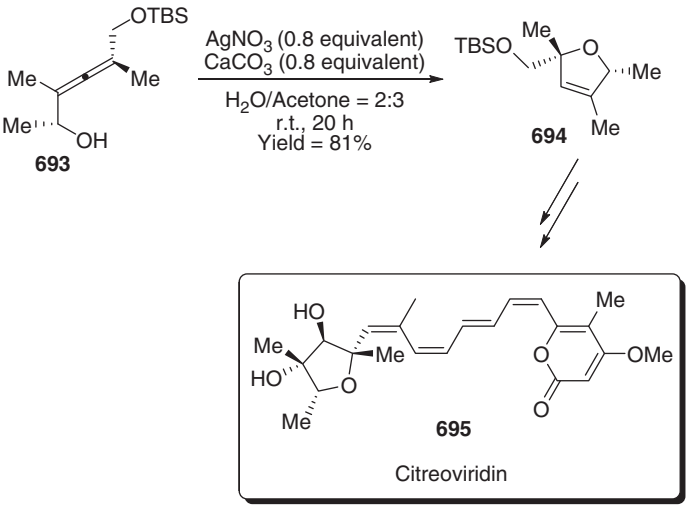


Scheme 175

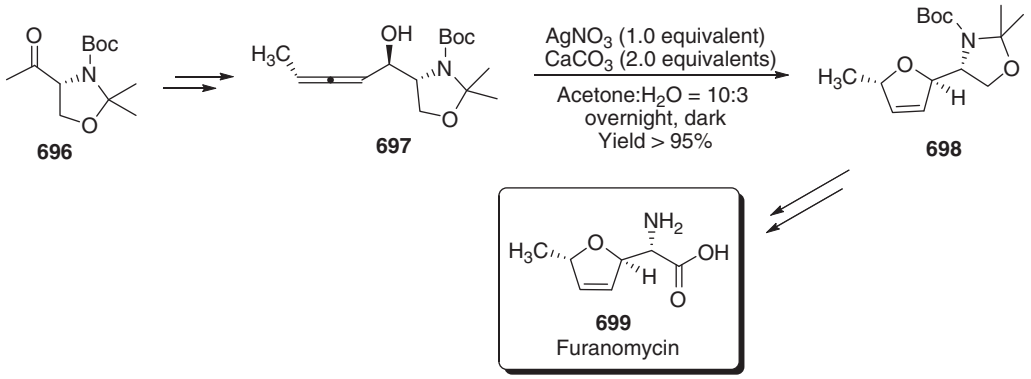
The cytotoxic amphidinolide **702** has been obtained by a Claesson's cyclization of 6-methylnona-4,5-dien-1,3-diol, derived from a chiral epoxyalcohol produced by the Sharpless asymmetric epoxidation (Scheme 178).[192] The allene alcohol was treated with $AgNO_3/CaCO_3$ in aqueous acetone to afford the corresponding dihydrofuran with strict chirality transfer.

As the first approach toward the cembranoid eunicin, a silver-mediated cyclization of a suitable functionalized allene was performed with the aim of controlling the stereochemistry in the construction of the tetrahydropyran ring (Scheme 179).[193] The *trans*-bicyclic dihydro-2*H*-pyran within the tricyclic framework of eunicins was obtained from silver nitrate-promoted cyclization.

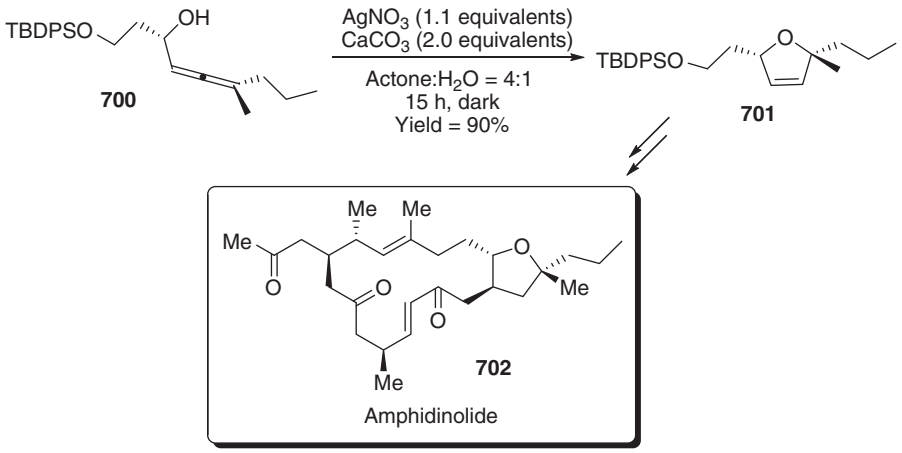
The tetradecane ring system of the anticancer and antiparasitic bielschowskysin was ingeniously built up through a stereoselective [2 + 2] photocycloaddition of an alkenyl alkylidenebutenolide. Silver-catalyzed cyclization of the corresponding ynenoic acid is used for the construction of γ-alkylidene butenolide (Scheme 180).[194]



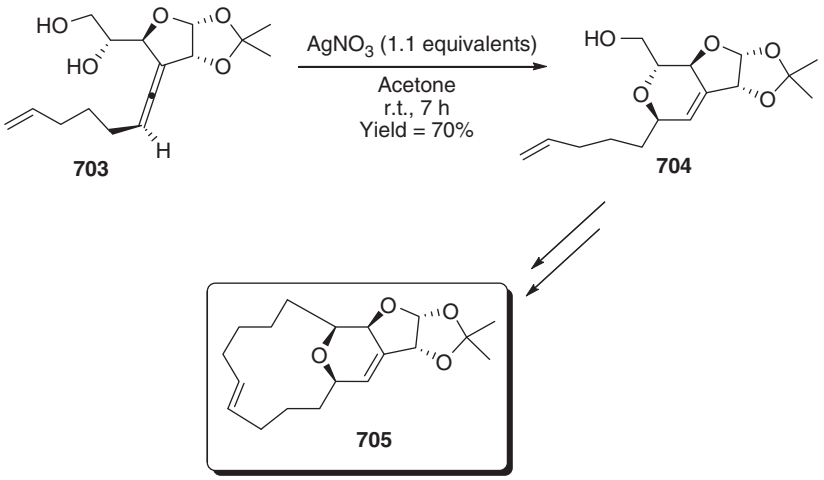
Scheme 176



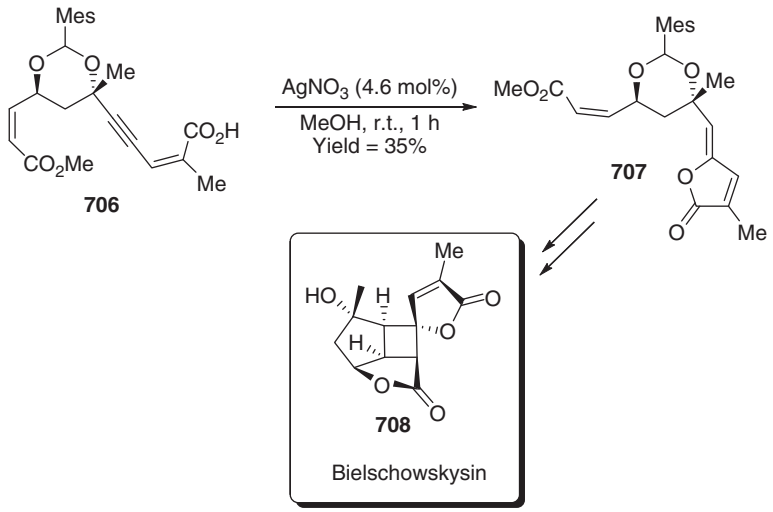
Scheme 177



Scheme 178



Scheme 179



Scheme 180

β-Allenic acids are used for the synthesis of δ-lactones in the presence of $AgNO_3$ and DIPEA. The reaction is proved to be an efficient asymmetric synthesis of the naturally occurring antibiotic (–)-malyngolide (Scheme 181).[195]

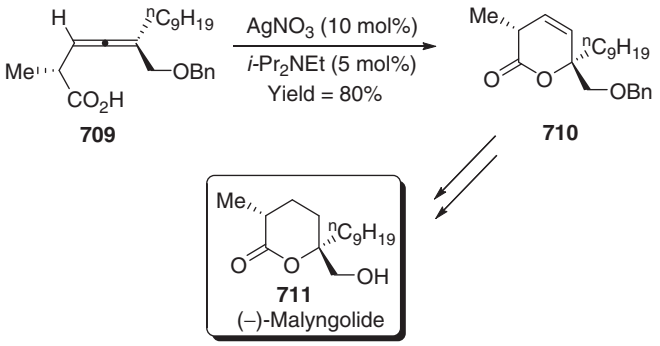
The cyclization of α-allenones was also successfully applied in the total synthesis of natural products. The furanocembranes, kallolide A, is obtained through Ag-catalyzed cyclization via key steps, using a catalytic amount of $AgNO_3$ in acetone, which led to a key furan building block in good yields.[196] The same strategy is applied in the synthesis of kallolide B (Scheme 182).[196]

In the total synthesis of (+)-longifolicin skeleton, sequential reactions of Pd-catalyzed hydrocarbonylation of a chiral homopropargylic mesylate and Ag^+-catalyzed cyclization of the intermediate allenic acid are carried out, and the desired product is successfully obtained (Scheme 183).[197]

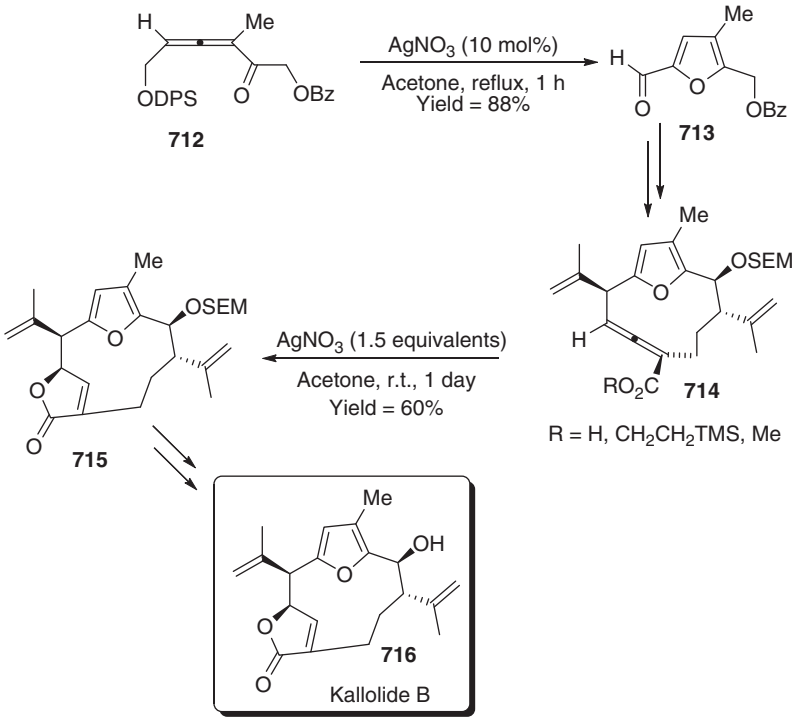
Nagarajan and coworkers developed an efficient methodology for the synthesis of highly functionalized ellipticinium and ellipticine derivatives via an AgOTf-catalyzed cyclization of 2-alkynyl-3-carbazolylaldimines (Scheme 184).[198]

The total synthesis of clavepictines was skillfully designed and realized with Ag^+-catalyzed cyclization of a piperidinoallene as the key step affording the desired *cis*-quinolizidine derivative in 48% yield (7% of vinyl isomer is obtained) (Scheme 185).[199] When the substrate is modified, the cyclization yield is significantly improved as well as the diastereoselectivity, and no other isomer could be detected.

During the synthesis of the antibiotic anisomycin, Ag-catalyzed cyclization of an alkoxyaminoallene was the key step (Scheme 186).[200]



Scheme 181



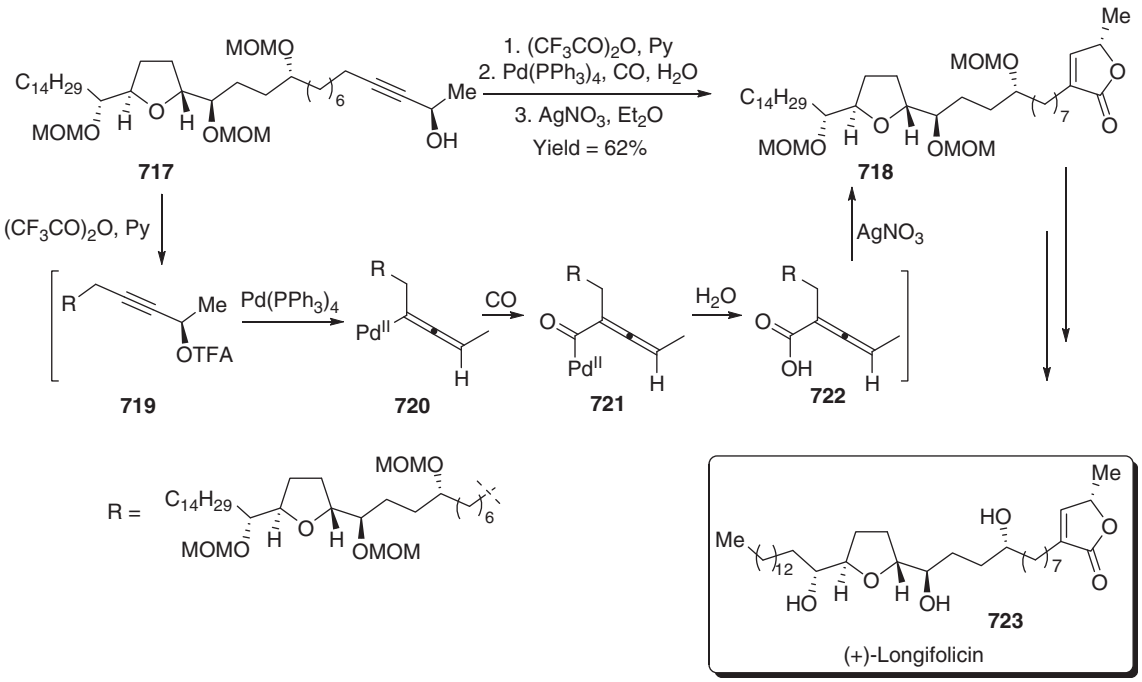
Scheme 182

4.07.4.3 Au- and Pt-Catalyzed Cyclization

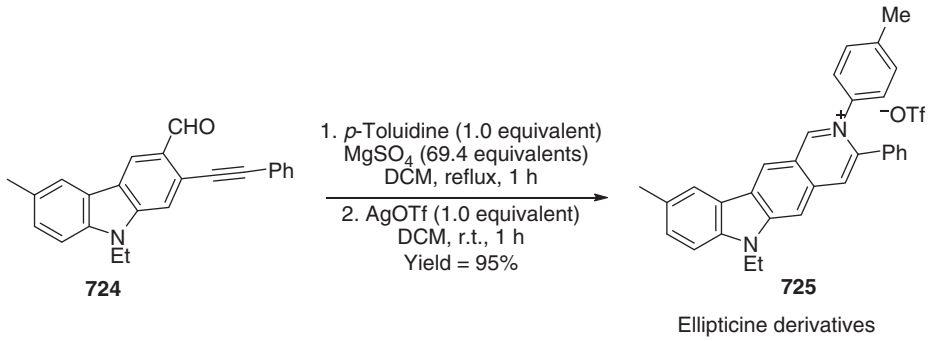
Pt and Au [gold(III) and cationic gold(I)] show an exceptional ability to accelerate a variety of organic transformations of unsaturated precursors. These processes result from the peculiar Lewis acid properties of these metals: the alkynophilic character of these soft metals and the π-acid activation of unsaturated groups promote the intra- or intermolecular attack of a nucleophile. Due to the soft and carbophilic character, gold and platinium catalysts are particularly well suited for the selective activation of allenes in the presence of other reactive functionalities. In the past decades, great progress has been achieved in developing efficient and selective Au- and Pt-catalyzed transformations, and prodigious number of reviews are available on various aspects.[201] This section is focusing on Au-catalyzed particular classes of synthetic reactions applied in total synthesis.

The first total synthesis of the β-carboline alkaloids (–)-isocyclocapitelline and (–)-isochrysotricine by Pictet–Spengler reaction of a chiral THF with tryptamine is reported by Volz and Krause (Scheme 187).[202] Key intermediate 2,5-dihydrofuran was obtained from the corresponding α,β-dihydroxyallene with complete axis-to-center chirality transfer by the use of only 0.05 mol% of gold(III) chloride in THF.

Erdsack and Krause used Garner's aldehyde as a precursor for α-hydroxyallenes, treated with 1 mol% of gold(III) chloride in THF, which undergo cycloisomerization to the dihydrofurans derivates. Subsequent modification affords analogs of the antibiotic amino acid furanomycin (Scheme 188).[203]



Scheme 183



Scheme 184

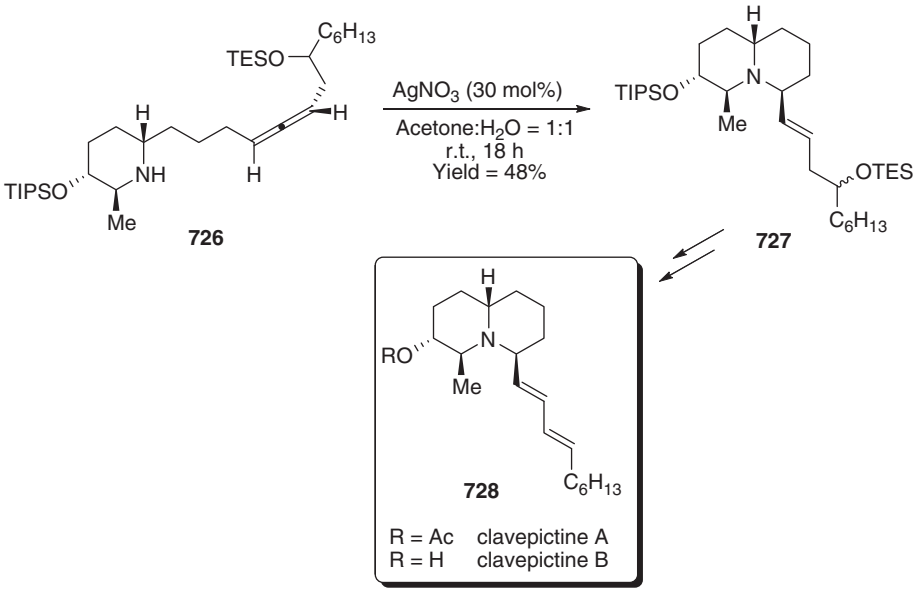
Krause and coworkers accomplished the first diastereo- and enantioselective total synthesis of (*R*,*R*,*R*)-bejarol and its (3*R*,5*S*,9*R*)-isomer. The gold-catalyzed cycloisomerization is used as a key step, which converts the enantiomerically pure *β*-hydroxyallenes **739**/**740** to the corresponding dihydropyrans **741a**/**741b** (Scheme 189).[204] A cationic gold catalyst is used for activating the allene for nucleophilic attack of the pyrrole ring to deliver tetrahydroindolizine in a high yield with excellent chirality transfer, which is the precursor of alkaloid (–)-rhazinilam (Scheme 190).[205]

In the Construction of the Communesin Ring, Funk and coworkers treated the alkyne **748** with $AuCl(PPh_3)$ to provide the enamine **749** via a 7-*exo-dig* ring closure with the nearby piperidine nitrogen (Scheme 191).[206]

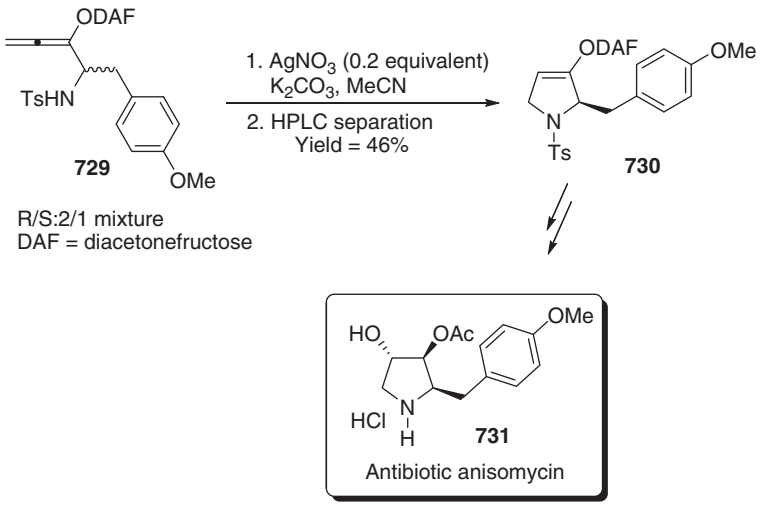
Oh and coworkers reported a Pt-catalyzed domino process involving a Huisgen-type [3 + 2] cyclization and subsequent insertion of the proposed platinum carbene intermediate into a benzylic bond to form highly complicated products that are difficult to access by other means. Byproducts **753** and **754** are obtained with $PtCl_2$, $PtCl_4$ in toluene, or $PtCl_2(PPh_3)_2$ in DCE or dioxane. A possible pathway through a platinum carbene intermediate is proposed for the three products in Scheme 192.[207]

4.07.5 Conclusion

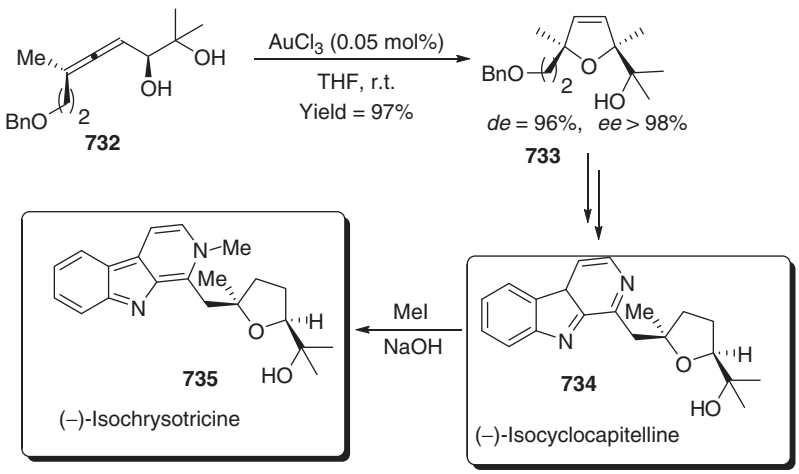
The electrophilic cyclization reaction is one of the most classic organic reactions. There are a huge number of works reported in the literature, and it is difficult to cover all of them. As so many methodologies were developed to construct all kinds of rings, the



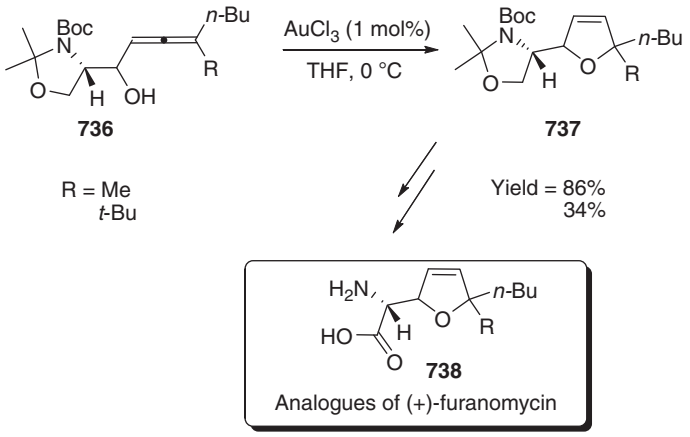
Scheme 185



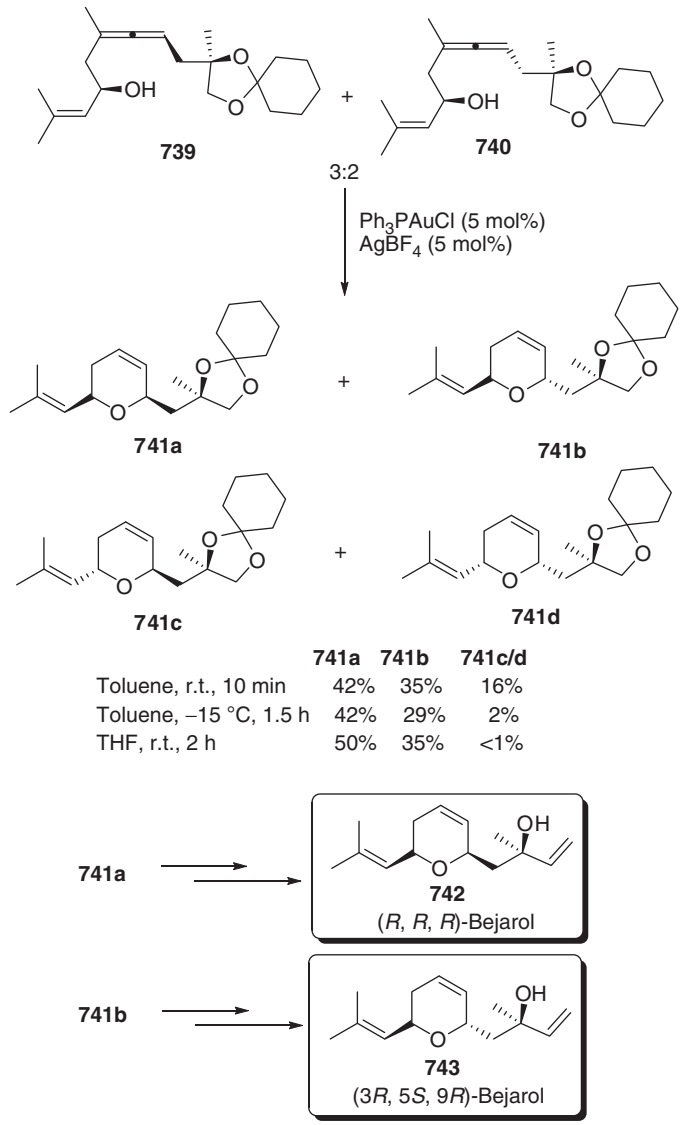
Scheme 186



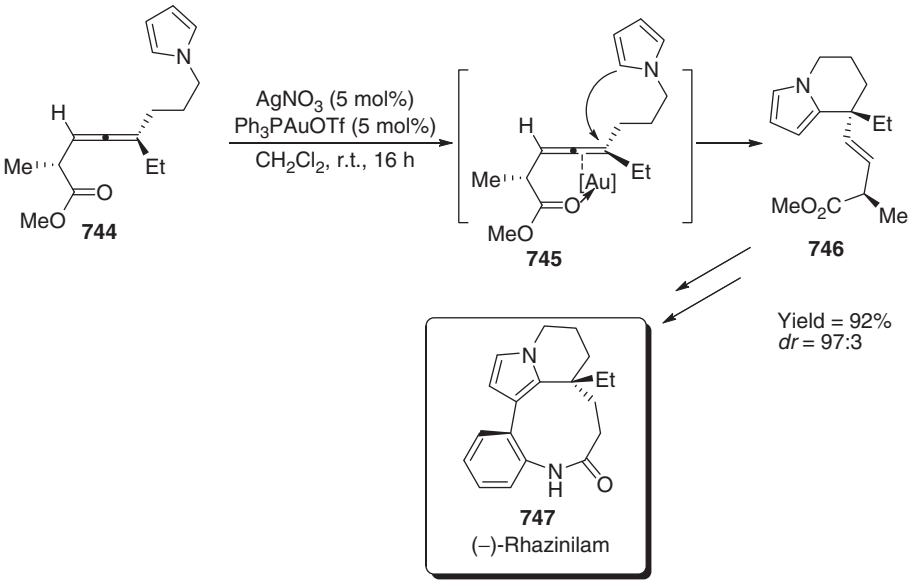
Scheme 187



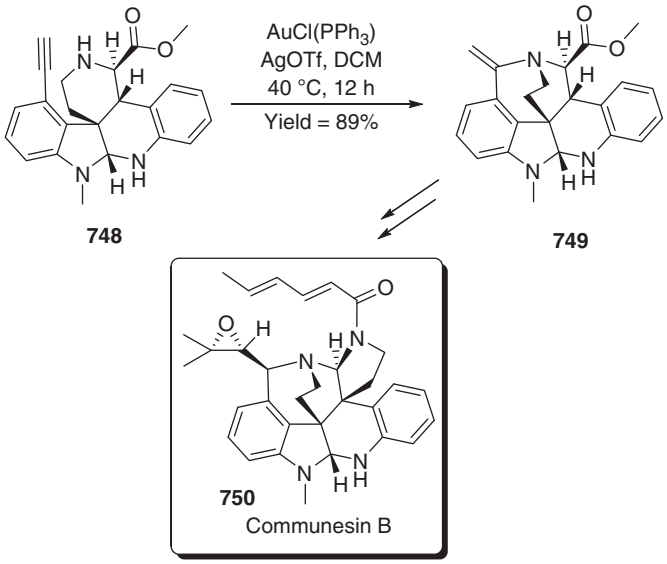
Scheme 188



Scheme 189

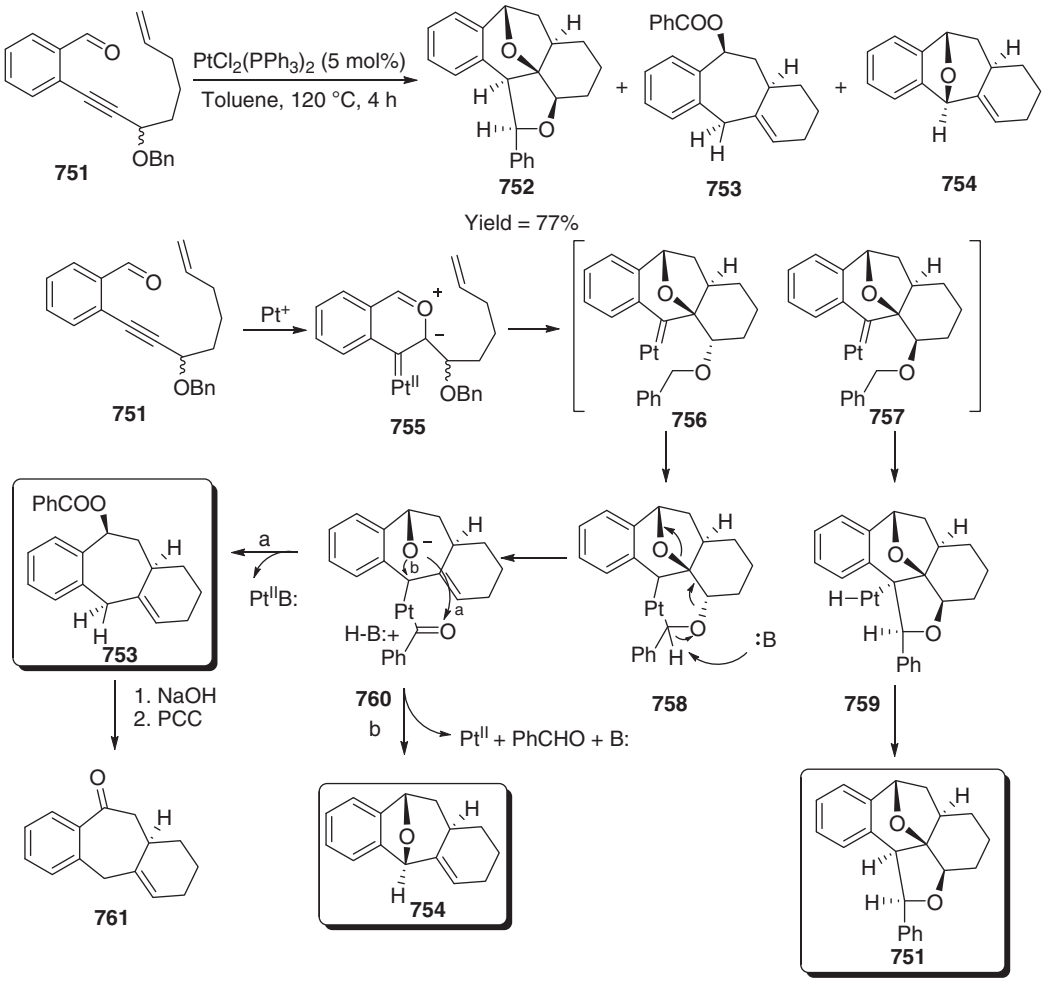


Scheme 190



Scheme 191

electrophilic cyclization becomes a valuable tool in organic chemistry. In recent years, the research on halocyclization is focusing on asymmetric methodologies and applications in natural product synthesis. Fluorocyclization has coursed more attention due to the excellent bioactivity of fluoro-containing molecules. Selenocyclization, tellurolactonization, and sulfenylcyclization have proved to be very efficient in introducing S, Se, and Te elements into the target molecules. Besides the traditional electrophiles mentioned in Sections 4.07.2 and 4.07.3, transition metal-mediated electrophilic-type cyclizations have been developed. The transition metal playing as a π-acid catalyst could also activate C–C multiple bond via coordination inducing the electrophilic-type cyclization. The applications of mercury-catalyzed electrophilic cyclization and silver-, gold-, and platinum-catalyzed electrophilic cyclization in natural product synthesis have been summarized. Palladium-induced electrophilic cyclization is also a very powerful tool in the synthesis, and there are lots of reviews presented in recent years,[208] which should be the topic of another big chapter. Lewis acid and Brønsted acid could also induce the electrophilic cyclization, and numerous applications in the synthesis of natural products have been reported in recent years.[209] These reviews could draw an outline for electrophilic cyclization in a different way.



Scheme 192

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4.08 Carbon–Carbon Bond-Forming Reactions Involving Aryl Radicals

SG Hammer and MR Heinrich, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

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Glossary

Aryl radical Arene compound with one free carbon-centered radical as part of the ring system. The phenyl radical ($C_6H_5^{\bullet}$) is the parent compound for aryl radicals.

Gomberg–Bachmann reaction Aryl–aryl coupling reaction proceeding via aryl radicals generated from aryl diazonium salts. Due to the high reactivity of aryl radicals, the reaction often also yields the reduced byproducts which arise from hydrogen abstraction.

Meerwein reaction Alkene functionalization usually proceeding via the addition of an aryl radical, generated from an aryl diazonium salt, to an alkene and trapping of the alkyl radical adduct by a heteroatom-centered radical scavenger. The heteroatom or group introduced in the second step may undergo elimination to give an aryl vinyl compound.

Pschorr reaction Intramolecular version of the Gomberg–Bachmann reaction. Due to the intramolecular reaction course, usually higher yields and regioselectivities are obtained in the Pschorr than in the Gomberg–Bachmann reaction.

Sandmeyer reaction Classical reaction to convert aryl diazonium salts, via aryl radicals, into aryl chlorides, bromides, or iodides. The scope has meanwhile been extended toward the introduction of many other functional groups.

4.08.1 Introduction

The most critical factor determining the scope and the limitations of reactions proceeding via free aryl radicals certainly is the high reactivity of these radicals toward many types of organic molecules. Together with alkenyl and alkinyl radicals, aryl radicals belong to the group of least-stabilized carbon-centered radicals.[1] The low degree of stabilization can easily be rationalized by bearing in mind that the sp^2-orbital, in which the unpaired electron of the radical is located, has a perpendicular orientation toward the π system of the aromatic core. In turn, no significant delocalization of the aryl radical is possible. Benzylic radicals, which in terms of stabilization represent more or less the complete opposite of aryl radicals, are very well stabilized due to the possible overlap of the radical-containing p-orbital with the aromatic π system. As a result, benzylic radicals behave like 'lazy' radicals, which often tend to dimerize rather than adding to an alkene or arene. Aryl radicals, however, are those reactive even with respect to hydrogen abstraction from C–H bonds, that the use of a number of organic solvents is not recommended for reactions proceeding via free aryl radicals.[2] These solvents include such common ones as tetrahydrofuran, ethanol, or diethyl ether.

The development of aryl radical chemistry throughout the past 130 years is somehow related to this reactivity issue. Given that the coupling of the aryl radical to a particular substrate is very fast, with rate constants k higher than $10^8\ M^{-1}\ s^{-1}$ up to diffusion control, the desired transformations are often quite easy to conduct. Since this is the case for many Sandmeyer-type reactions, in which, for example, chlorine or bromine atoms are transferred from a copper(II) salt to an aryl radical, it appears comprehensible why this reaction type has been discovered as early as 1884.[3,4] The critical key step of the Gomberg–Bachmann reaction (1924),[5]

which is the addition of an aryl radical to a substituted benzene, proceeds with an approximately 100-fold lower rate constant of $k \sim 10^6\ M^{-1}\ s^{-1}$.[6,7] To counterbalance the disadvantage of the comparably low rate constant and to limit potential side reactions, the substrate for the aryl radical often has to be present in large excess and is commonly used as solvent. Not surprisingly, this special requirement has led to quite narrow scope of Gomberg–Bachmann reactions.

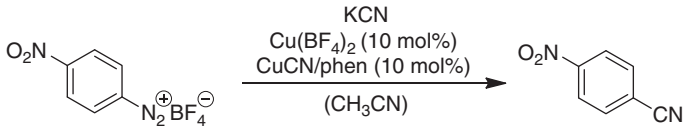
In Pschorr cyclizations (1896),[8] which represent the intramolecular version of Gomberg–Bachmann reactions, the addition of the aryl radical to the other aromatic system is far less problematic due to the intramolecular setup and the resulting proximity of the reaction centers.[9] As a consequence, the aryl radical is often rapidly trapped in the desired way and solvents can be chosen from a broader range without having to encounter hydrogen abstraction by the aryl radical.

Knowing about the central importance of the rate constants associated with the key steps of the above-mentioned basic reaction types, it is not difficult to understand why the Meerwein reaction (1939) was first discovered for activated alkenes.[10] Additions of aryl radicals to such activated alkenes including acrylates, vinyl ketones, styrenes, and acrylonitriles proceed with sufficiently high rate constants of $k \sim 10^8\ M^{-1}\ s^{-1}$ to limit potential side reactions.[11] Nonactivated alkenes, such as hexene, are generally attacked by the aryl radical approximately one order of magnitude more slowly ($k \sim 10^7\ M^{-1}\ s^{-1}$), which makes the choice of solvents and reaction conditions more difficult.[12]

In this chapter it will be shown how the scopes of Pschorr, Gomberg–Bachmann, and Meerwein-type reactions have been expanded over the recent years. Related to this introductory section, we will see that many of those developments are either associated with the discovery of new and efficient traps for aryl radicals, with the control of side reactions by carefully choosing reaction conditions or with rate acceleration by conducting the transformations rather intramolecularly than intermolecularly. In addition, new aryl radical sources have emerged next to the classical aryl diazonium salts and also the well-known aryl halides. These new aryl radical precursors include arenes and heteroarenes bearing functional groups such as hydrazines, boronic acids, azosulfides, diazotates, triazenes, or azocarboxylates.

4.08.2 Aryl Radical Addition to Cyanide and Carbanions – Nucleophilic Aromatic Substitutions

The probably most simple way to achieve a carbon–carbon bond formation via aryl radicals is to conduct the Sandmeyer reaction with copper cyanides instead of the commonly used copper chlorides or bromides. The particular reaction type that introduces nitrile groups into arenes has already been described by Sandmeyer himself in 1884.[3,4] A representative example from a recent report on the synthesis of benzonitriles is shown in Scheme 1.[13] In this modern Sandmeyer-type protocol, catalytic amounts of copper salts are used in combination with the ligand 1,10-phenanthroline and potassium cyanide.



1 **2** (93%)

Scheme 1 Synthesis of benzonitrile **2** from aryl diazonium salt **1** using a Sandmeyer reaction.[13] Reproduced from Beletskaya, I. P.; Sigeev, A. S.; Peregudov, A. S.; Petrovski, P. V. *J. Organomet. Chem.* **2004**, *23*, 3810–3812.

Several mechanisms have been proposed for Sandmeyer reactions.[2] Hereby, there is general agreement on the fact that aryl radicals are generated from the reduction of the aryl diazonium ions by copper(I) salts and subsequent loss of nitrogen. For the following transfer of the halogen atom or, as in our case, that of the cyano group two pathways are basically possible. One of those pathways proceeds via the addition of the aryl radical to copper(II)-cyanide and subsequent reductive elimination from the resulting copper(III)-intermediate to give the benzonitrile and copper(I)-cyanide (*see* Chapter 1.04). Alternatively, the cyano group can be directly transferred from the copper(II)-salt to the aryl radical. Byproducts such as symmetrical biphenyls are more plausible according to the mechanism involving copper(III)-intermediates, since free aryl radicals usually do not have sufficiently long lifetimes to undergo dimerization reactions. The formation of azobenzenes similar to homocoupling of an aryl radical to its parent diazonium salt has been observed in reactions in which no potentially coordinating metal ions are present. These byproducts are therefore more likely produced through the free-radical mechanism involving a cyanide transfer from copper(II)-cyanide.

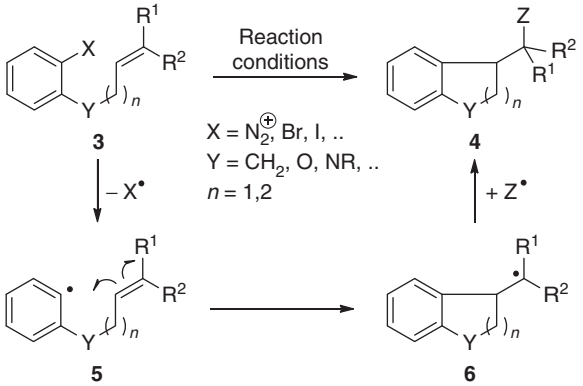
Aryl radical-substitution reactions of carbanions usually proceed according to a $S_{RN}1$ mechanism and they can thus be also described as nucleophilic aromatic substitutions. Comprehensive reviews on this topic have been compiled by Rossi et al.[14] Mainly under photochemical irradiation, aryl radical sources such as aryl halides, diaryl sulfides, and arylazosulfides can react with a vast variety of carbanions derived from hydrocarbons, ketones, carboxylic acids and esters, *N*,*N*-disubstituted amides, thioamides, imides, β-dicarbonylic compounds, nitriles, nitroalkanes as well as cyanide to achieve carbon–carbon bond formation (*see* Chapter 9.13). Two representative examples are phenylations of the enolate derived from acetone with diphenylsulfides[15] or arylation of the dianion derived from phenylacetic acid with iodo- and bromobenzenes,[16] among which the latter shows a remarkable selectivity dependence on the counterion.

4.08.3 Meerwein-Type Reactions: Aryl Radical Addition to Double and Triple Bonds

4.08.3.1 Intramolecular Addition–Cyclization Reactions

4.08.3.1.1 Cyclization onto C–C double bonds

Cyclization reactions, as they are depicted in a general way in Scheme 2, have become a common tool to evaluate new sources of aryl radicals, new reaction conditions for their generation, as well as new trapping reagents for either aryl or alkyl radicals.[17] The cyclization reaction of **3** into **4**, which can also be employed as a radical clock in competition experiments, benefits from the extremely rapid intramolecular addition of the aryl radical **5** to the alkene ($k=5\times10^8$ s^{-1} for $n=1$, Y=CH_2) in the cases that five- or six-membered rings **6** are formed ($n=1$, 2).[18] The high rate constant for the cyclization step leads to an effective minimization of undesired side reactions, such as hydrogen abstraction from solvents. A further acceleration of the cyclization is possible by exploiting the Thorpe–Ingold effect and replacing a methylene unit in the side chain (Y=CH_2) by, for example, an oxygen atom ($k=8\times10^9$ s^{-1} for $n=1$, Y=O). Additional radical-stabilizing substituents in the positions R^1 and R^2 have a comparable effect on the rate of the cyclization step.



Scheme 2 Intramolecular Meerwein reactions for the evaluation of new radical sources, trapping reagents, and reaction conditions.

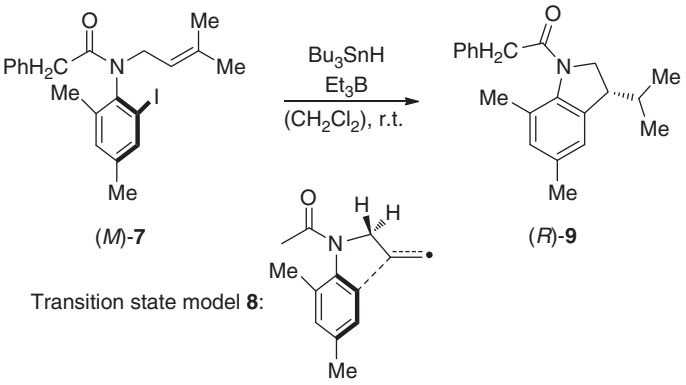
Meerwein-type cyclization reactions of aryl diazonium salts (**3**, X=N_2^+) can be initiated with such diverse reagents as sodium iodide,[19] thioacetates,[20] copper salts,[21] organotin reagents,[22] or strong organic reductants.[23] When starting from aryl bromides (**3**, X=Br), organotin hydrides,[24] titanium complexes,[25] and alkylboranes[26] have been found to be effective and useful reagents. Recently, such cyclization reactions have also been successfully conducted in a microreactor.[27] Due to the easily cleavable carbon–halogen bond in aryl iodides, aryl radicals can be generated from these precursors under an even broader variety of reaction conditions (**3**, X=I). In addition to simple irradiation,[28] organodistannanes,[29] samarium diiodide,[30] cobalt complexes,[31] and other reductants[32,33] are today commonly used to prepare products such as indanes, dihydroindoles, or dihydrobenzofurans (*see* Chapter 1.09). As mentioned before for aryl bromides, new types of strong organic electron donors are currently emerging as powerful replacements for the metal-based reagents.[34]

Cyclization precursors or aryl radical sources, which have so far been reported in pioneering studies, are trifluoroborates (**3**, X=BF_3^-)[35] and azocarboxylates (**3**, X=N_2COOR).[36]

Besides the different aryl radical precursors, which are applicable for Meerwein cyclizations, this reaction has been intensively investigated with respect to possible ring sizes,[37] regioselectivity,[38] undesired side reactions such as hydrogen transfer[39] as well as unusual and unexpected cyclization types.[40]

Although the choice of the substituent X, from which the aryl radical is generated, does not have an effect on the structure of the product **4**, the scope of Meerwein-type cyclization reactions can be broadened by new trapping reagents introducing atoms or functional groups Z. In the simplest case, a hydrogen atom is transferred to the alkyl radical **6** arising from the cyclization step, so that the overall reaction can be classified as reductive cyclization. Organotin hydrides have been found to be useful reagents for this purpose, since the tin hydride can generate aryl radicals from aryl bromides or aryl iodides via the related stannyl radical, and as well deliver a hydrogen atom to the alkyl radical intermediate. A major problem of most reactions using organotin hydrides is, however, the difficult removal of the resulting organotin species from the product mixture, which makes these transformations significantly less attractive. Improved versions of tin hydride-based reductive radical cyclizations use water-soluble organotin hydrides in combination with water-soluble derivatives of the initiator 2,2'-Azobis(2-methylpropionitrile) (AIBN).[41] In this way, the tin-containing species can be easily separated from the desired products by aqueous extraction during work-up.

An interesting application of Meerwein-type cyclization reactions developed by Curran and coworkers[42] is the transfer of axial chirality into central chirality. A recent example from this group of transformations is depicted in Scheme 3.[43] In this reaction, aryl radicals are generated from an iodinated acetanilide **7** using tributyltin hydride combined with the low-temperature radical



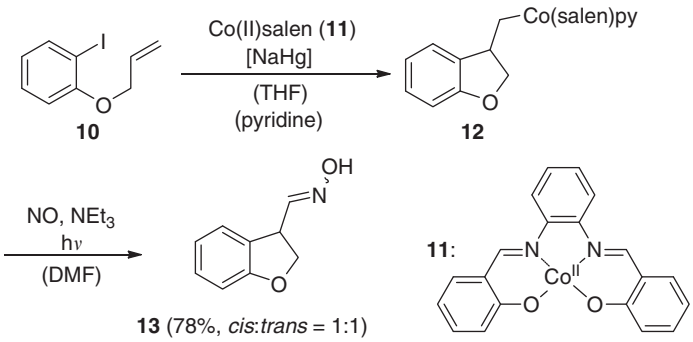
Scheme 3 Transfer of axial chirality into central chirality through a Meerwein-type cyclization.[43]

initiator triethylborane. The predetermined conformation of **7** forces the reaction to pass via a well-defined transition state **8**, through which the configuration at the new stereocenter of the dihydroindole **9** is established with high selectivity.

Cyclization reactions, in which the cyclic adduct radical is further oxidized and not reduced, have recently been reported by Rueping et al.[44] This reaction course finally leading to benzofurans can be achieved by conducting the cyclization of 2-iodophenyl allyl ethers in the presence of potassium *tert*-butoxide and 1,10-phenantroline (phen).

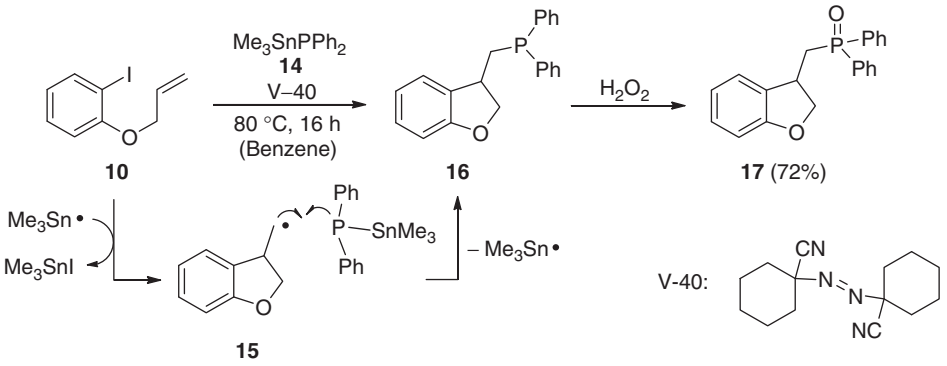
Far more structural diversity than from reductive reactions can be attained by trapping the alkyl radical arising from the cyclization step by carbon-centered radical scavengers. Reagents that have been found especially useful for this purpose are electron-poor, acceptor-substituted – we will further on call them activated – alkenes such as acrylic esters, styrenes, vinyl sulfones, or acrylonitrile.[45] These radical reactions, which have the rare feature that two carbon–carbon bonds are formed to an alkene, absolutely rely on the partially intramolecular setup. Only due to the cyclization step, the typical reactivity order of aryl radicals toward alkenes can be inversed and the aryl radical attack can first be directed to the nonactivated alkene (cf. **5** to **6**, Scheme 2). In the next stage, the adduct radical **6** then adds selectively to the also available activated alkene. Aryl radical generation in the presence of an activated (e.g., methyl acrylate) and a nonactivated alkene (e.g., 1-hexene), for comparison, would result in approximately 10-fold faster addition of the radical to the activated substrate.[46] Besides activated alkenes, carbon monoxide can be used to trap cyclized radicals **6**.[47] Aryl radical generation by reduction with samarium(II)-iodide and trapping of the cyclized radical by another molecule of samarium(II)-iodide allows further reactions with electrophiles such as ketones.[48] The result is a radical–polar crossover reaction type whose second ionic step is comparable to a Grignard reaction.

When the radical cyclization of an allylphenylether **10** is conducted in the presence of a suitable cobalt complex **11**, the alkyl radical resulting from the cyclization step is readily trapped by the cobalt complex to give an organocobalt compound **12** (Scheme 4).[31,49] Due to the ability of many organocobalt species to give radicals under mild conditions, intermediates such as **12** are versatile precursors for the introduction of a variety of heteroatoms through radical reactions with a variety of scavengers. In addition to reactions with nitrogen monoxide, which lead to nitroso compounds or oximes **13**, depending on the substitution of the α-carbon atom in the alkyl chain, the organocobalt compounds can alternatively be converted to alcohols, alkoxamines, thioethers, or sulfinic acids through trapping with molecular oxygen, TEMPO, disulfides, or sulfur dioxide, respectively.[31]



Scheme 4 Cyclization and nitrosation through an organocobalt intermediate.[31]

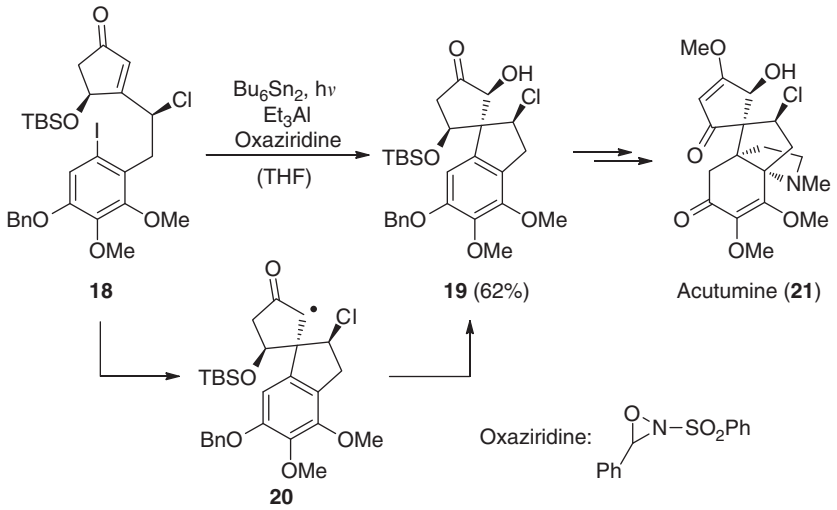
The introduction of phosphorus through trapping of the cyclized alkyl radical with trimethylstannyl diphenylphosphine **14** has recently been reported by Studer and coworkers[50] (Scheme 5). In contrast to the reductive cyclizations described above (cf. Scheme 3), in which hydrogen is transferred to the cyclized alkyl radical from reagents such as tributyltin hydride, the alkyl radical **15** now induces a radical substitution on the phosphorus atom to liberate an organostannyl radical. This stannyl radical is of



Scheme 5 Cyclization and radical addition to phosphorus.[50]

importance since it can generate a new aryl radical from the iodinated phenylether **10**, thereby closing the radical chain. Due to the generally low stability of alkyl phosphine functionalities toward oxidation, the dihydrobenzofuran **16** was further converted to the phosphine oxide **17** for characterization.

A beautiful example for an application of a Meerwein-type cyclization in natural product synthesis is shown in Scheme 6.[51,52] The aryl radical generation from iodobenzene **18** with hexabutyldistannane under irradiation is followed by an intramolecular addition (5-exo-type spirocyclization) onto a vinyl ketone, which belongs to the group of activated alkenes. The high rate of the cyclization step becomes obvious from the fact that even tetrahydrofuran could be used as solvent. Tetrahydrofuran is known as an efficient hydrogen donor and does otherwise readily stabilize aryl radicals by hydrogen transfer. The overall transformation of **18** into **19**, including the introduction of the hydroxyl group, can be classified as a radical–polar crossover process. Hereby, triethylaluminium promotes the conversion of the cyclized radical **20** into the corresponding enolate and the oxaziridine serves as hydroxylating agent.



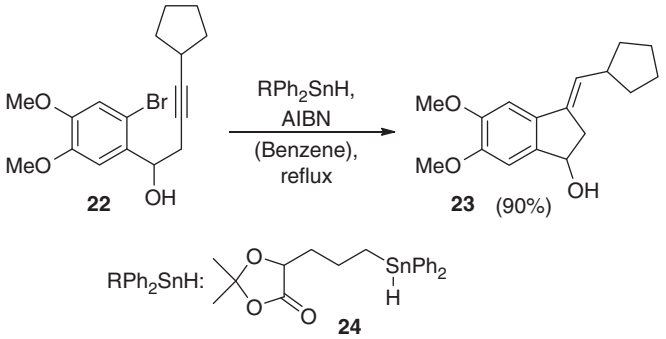
Scheme 6 Meerwein-type cyclization as key step in the total synthesis of acutumine (**21**).[52]

A number of further natural products or natural product substructures have been prepared using Meerwein-type cyclization reactions. These include lennoxamine,[53] (−)-aphanorphine,[54] mappicine ketone,[55] argemonine,[56] and penitrems.[57]

4.08.3.1.2 Cyclization onto C–C triple bonds

Compounds with carbon–carbon triple bonds are far less frequently used as acceptors for aryl radicals than alkenes. Although the rate of addition of an aryl radical to a triple bond is not significantly slower than that to a double bond, difficulties can arise from the fact that a highly reactive vinyl radical is generated in the addition step, which is itself sometimes difficult to control.[12]

A recent example for a Meerwein-type cyclization onto a triple bond is depicted in Scheme 7.[58] After the cyclization of **22** into **23** has been completed, the particular organotin hydride **24** used in the reaction can be easily converted into an α-hydroxy carboxylic acid under basic conditions. This later allows an easy separation of the tin-containing species by basic extraction during work-up. The above-mentioned potential difficulty with reactive vinyl radical intermediates arising from the cyclization does not



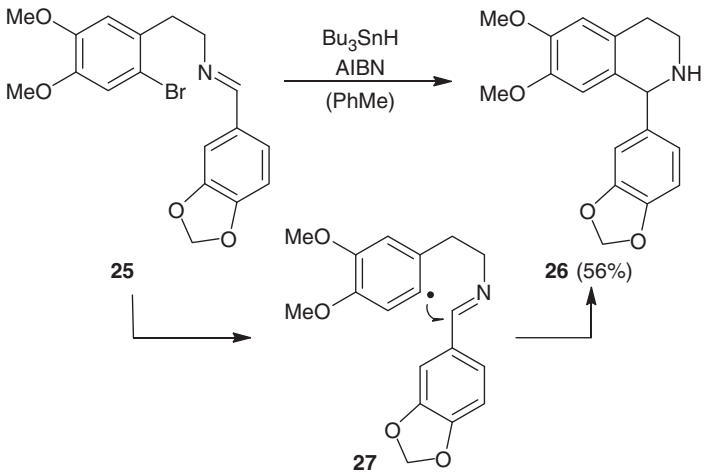
Scheme 7 Meerwein-type cyclization onto a carbon–carbon triple bond.[58]

usually play a role in reactions with tin hydrides, since these radicals are rapidly reduced by the tin hydride and side reactions are effectively suppressed.

A study on the radical cyclization of a phenylpropargyl ether has also recently been reported.[59] In the presence of the strong reductant samarium(II)-iodide, the resulting 3-(methylene)benzodihydrofuran is, however, rapidly further reduced to the methyl-substituted heterocycle.

4.08.3.1.3 Cyclization onto C–het double and triple bonds

The intramolecular addition of an aryl radical onto an imine can occur at the imine's nitrogen or carbon atom. Important factors influencing the regioselectivity of the attack are the size and possible strain of the newly formed ring system, the presence of stabilizing substituents for the cyclized radical, as well as steric factors.[60] A representative example, in which an imine is preferably attacked at its carbon atom and thus a new carbon–carbon bond is formed, is shown in Scheme 8.[61]

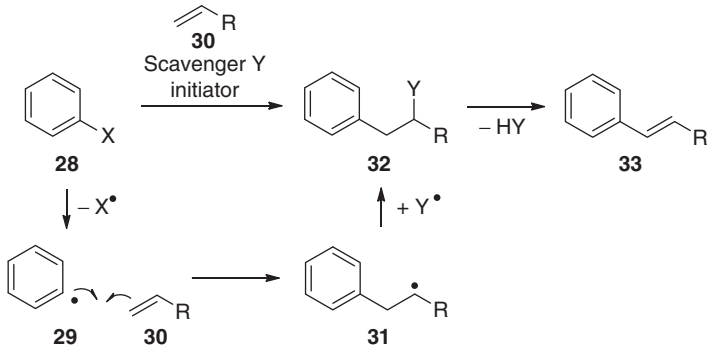


Scheme 8 Cyclization of **25** through an intramolecular aryl radical attack onto an imine.[61]

Along with the tetrahydroisoquinoline **26**, also the *N*-benzyl indoline, which arises from the undesired attack of aryl radical **27** onto the nitrogen atom, was observed as a byproduct in 10% yield. By placing a second phenyl substituent on the carbon atom of imines such as **25**, the selectivity of this type of cyclization reaction can be completely reversed. Due to increased steric hindrance for the attack on the carbon atom and better stabilization of the radical adduct, indolines are then produced as main products. This strategy, where imines act as nitrogen-centered radical scavengers,[62] has recently also been employed for the enantioselective preparation of indolines.[63,64] A tandem cyclization including an intramolecular aryl radical attack onto the carbon-atom of a nitrile has been used for the synthesis of luotonin A.[65]

4.08.3.2 Intermolecular Addition

For several reasons, which are explained in more detail below, intermolecular Meerwein reactions are more difficult to conduct than the cyclization reactions shown above. This can be rationalized by a closer look at the key steps shown in Scheme 9.



Scheme 9 Key steps of intermolecular Meerwein reactions.

Starting from the aryl radical precursor **28**, the attack of the aryl radical **29** onto the alkene **30** is now no longer facilitated by the close proximity of the reacting centers. Therefore, the reactivity of the alkene **30** now plays a much more critical role, and special precautions have to be taken for alkenes with low reactivity or large steric hindrance. Considering alkene reactivity, as mentioned in the introductory section, it is easily comprehensible why activated alkenes such as acrylates, styrenes, vinyl sulfones, and vinyl ketones have for a long time been the preferred substrates in intermolecular Meerwein arylations. Although the aryl radical attack on activated alkenes is fast, which limits potential side reactions of the aryl radical, there is also one significant disadvantage. This drawback is related to the fact that most activated alkenes undergo oligo- or polymerization reactions far more readily than nonactivated alkenes as 1-hexene or allylic alcohol. To avoid the formation of polyaddition products, the scavenger Y has to be highly reactive toward the adduct radicals **31** to give **32**, but at the same time the aryl radical **29** should not be trapped directly by Y. Depending on the reaction conditions, the primarily formed Meerwein addition products **32** may undergo an elimination leading to vinyl benzenes **33**.

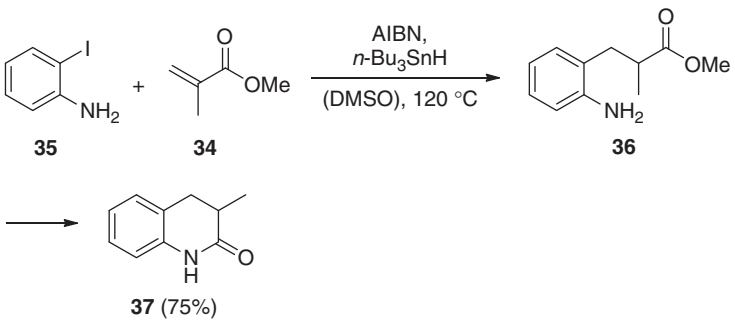
In the following Section 4.08.3.2.1, the scope and the limitations of intermolecular Meerwein reactions will be presented in the order of the atoms or functional groups that can be introduced through different scavengers Y.

4.08.3.2.1 Addition onto C–C double bonds

Intermolecular reductive Meerwein reactions differ considerably from the above-shown intramolecular versions. This is due to the circumstance that a scavenger Y representing a good hydrogen donor, such as tributyltin hydride, could preferably reduce the aryl radical **29** rather than the less-reactive alkyl radical **31** (Scheme 9). In intramolecular reductive reactions, the cyclization (**5** into **6**, Scheme 2) is usually fast enough to protect the aryl radical from direct reduction.

Given this difficulty, the reduction step in the intermolecular Meerwein reactions does ideally not occur in the sense of a hydrogen transfer to **31**. Early examples showing how to solve this problem have been reported by Citterio et al.[66] The key hereby is to conduct these transformations as radical–polar crossover processes. Under strongly reductive conditions, the adducts resulting from the aryl radical addition to substrates such as acrylic esters can be further reduced to enolates, which in summary corresponds to a reductive arylation. The critical steps of these reactions are hereby quite similar to those shown in Scheme 6, except that the enolate is just protonated and not further hydroxylated.

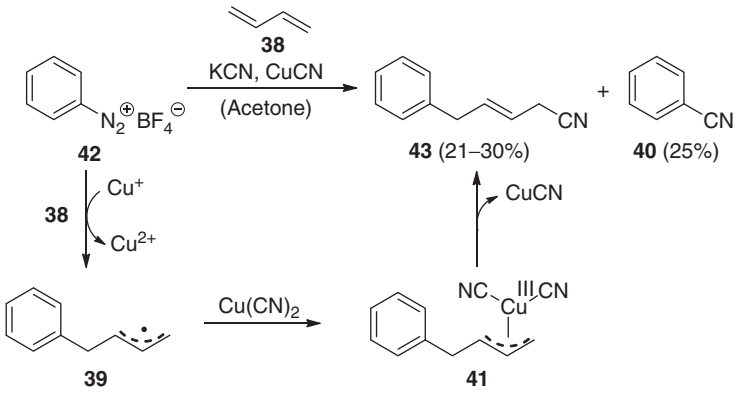
Owing to the requirement that the adduct **31** needs to be further reduced, only activated alkenes including acrylates, vinyl ketones, vinyl sulfones, vinyl phosphonates, and acrylonitrile have so far been found useful for intermolecular reductive Meerwein reactions.[67] A recent example of this reaction type is depicted in Scheme 10.[68]



Scheme 10 Reductive Meerwein arylation in the synthesis of 3,4-dihydroquinolinones.[68]

The reductive radical arylation of the acrylic ester **34** with *ortho*-iodoaniline **35** leads to the arylated ester **36**, which further cyclizes to give a 3,4-dihydroquinolinone **37**. Interestingly, only small amounts of aniline were observed as side product from the reduction of the intermediate 2-aminophenyl radical by tributyltin hydride. This is a promising result in the sense that organotin hydrides might not be highly reactive toward all types of aryl radicals. Furthermore, this finding could indicate that the hydrogen transfer from tributyltin hydride might be directed to the better-stabilized (less reactive) radical through a careful choice of the reaction conditions. Usually, aryl radicals are far more easily reduced by hydrogen atom transfer than stabilized α-methylcarbonyl radicals.[12]

The change from an intramolecular to an intermolecular reaction course does also complicate those Meerwein reactions in which the adduct radical **31** (Scheme 9) is to be trapped by a carbon-centered radical scavenger so that two carbon–carbon bonds are formed. Although a number of examples are known for the intramolecular version (*see* Section 4.08.3.1.1), only copper(I)-cyanide has so far been shown to be a suitable reagent to achieve an intermolecular cyanoarylation (Scheme 11).[69]



Scheme 11 Cyanoarylation of 1,3-butadiene (**38**).[69]

For the cyanoarylation, 1,3-butadiene (**38**) represents a very well-suited substrate. Comparable to styrenes, which give benzylic radicals on radical addition, 1,3-butadiene can be classified as an activated alkene due to the stabilized allylic radical **39** that is generated through the attack of the aryl radical. The fast addition step to the alkene is necessary to limit the formation of the Sandmeyer-type direct trapping product benzonitrile (**40**). Furthermore, the allylic radical **39** offers the unique possibility to transfer the cyano group via a copper(III)-intermediate **41**.[11b] So far, no other activated alkenes have been found to be applicable for Meerwein-type cyanoarylation reactions converting diazonium salts **42** in products comparable to **43**.

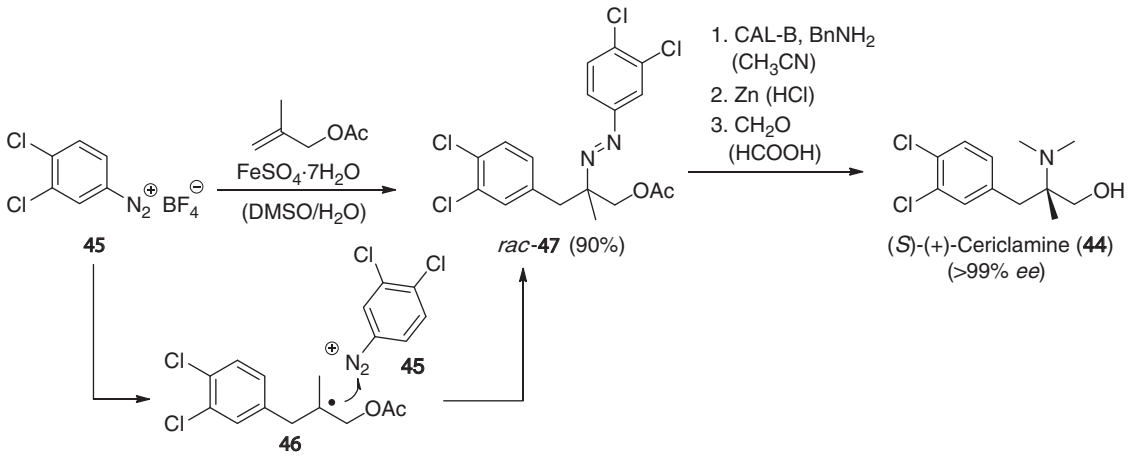
Meerwein reactions leading to carboamination require the trapping of the adduct radical **31** (Scheme 9) by a nitrogen-centered radical scavenger.[62] Since nitrogen-centered radical scavengers are more or less electrophilic and most aryl radical adducts of activated alkenes as well, the usually preferred group of activated alkenes is consequently not the first choice for carboamination reactions. Meerwein-type carboamination reactions can be conducted with activated alkenes such as acrylic esters, but the aryl radical attack has to be directed to the α-position of the α,β-unsaturated carbonyl compound by increasing the steric hindrance on the β-carbon atom.[70] In this way, a nucleophilic radical is formed on the β-carbon atom in the addition step, which can be trapped with a nitrogen-centered radical scavenger such as aryl diazonium salts. Due to the restrictive requirements concerning the substitution pattern of the activated alkene, the substrate scope of those reactions remains rather limited.

Carboamination reactions of nonactivated alkenes, in contrast, have turned out to be far more versatile. Based on early mechanistic studies, in which aryl diazonium salts had been discovered as nitrogen-centered radical scavengers for nucleophilic alkyl radicals,[71] radical carbodiazenlyation (or carboamination) reactions have recently been established as a versatile and reliable synthetic strategy.[72] Although first attempts to run these reactions in a diastereoselective manner using chiral auxiliaries led to only moderate selectivities,[73] kinetic enzymatic resolution turned out to be better suited for the preparation of enantioenriched carboamination products.[74] The synthetic sequence of a recent study, in which a radical carboamination reaction was used in combination with biocatalysis to prepare (+)-cericlamine (**44**), is depicted in Scheme 12.[75]

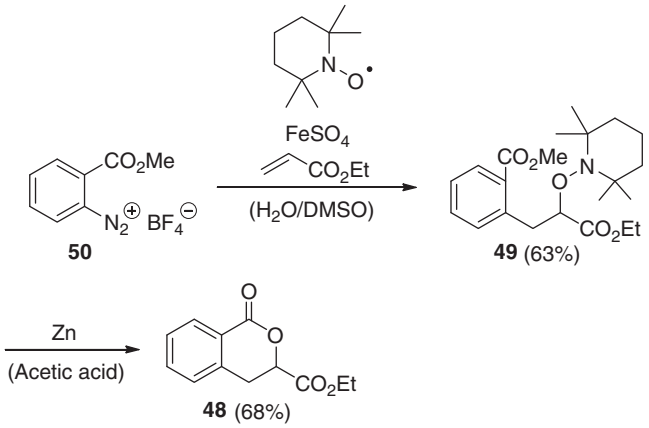
As in all carboamination reactions of this type, the diazonium salt **45** serves as aryl radical source and as scavenger for the alkyl radical intermediate **46**. The two phenyl groups in the azo compound **47** therefore come from the same precursor. A pioneering study on the applicability of nitrogen monoxide[76] as nitrogen-introducing reagent in Meerwein reaction recently revealed that this simple radical scavenger is well suited to achieve the carboamination of activated and nonactivated alkenes.[77]

Early examples for copper-mediated carbohydroxylation- and carboacetoxylation-type Meerwein reactions have been reported for the alkenes 1,3-butadiene and isoprene (*see* Chapters 6.03 and 8.13).[78] The reaction course and underlying mechanism are hereby similar to that shown in Scheme 11, including the restriction of the substrate scope to this specific group of activated alkenes.

Far more versatile are carboxygenation reactions using TEMPO as oxygen-centered radical scavenger.[79,80] Activated alkenes as well as nonactivated alkenes can be employed as reactants. To minimize the direct trapping of the aryl radical by TEMPO, the reactions are ideally conducted in a polar solvent. A representative example is depicted in Scheme 13.[80]



Scheme 12 Synthesis of (*S*)-cericlamine (**44**) through a combination of radical carboamination and kinetic enzymatic resolution.[75]



Scheme 13 Synthesis of oxoisochromane **48** through a radical carbohydroxylation sequence.[80]

The TEMPO adduct **49** that was formed from the Meerwein reaction of diazonium salt **50** and ethyl acrylate could easily be converted to the corresponding alcohol under reductive conditions. In the present example, reduction to the alcohol is accompanied by cyclization to lactone **48**. Meerwein-type carbohydroxylation reactions have also been achieved recently with aryl boronic acids,[81] aryl hydrazines,[82] and aryl azocarboxylates[83] as aryl radical precursors using oxygen gas as oxygen-centered radical scavenger. Therefore, the reactions had to be conducted under an oxygen atmosphere and the primarily obtained hydroperoxides were subsequently converted to the desired alcohols through a reductive step.

In carbothiolation reactions, the alkyl radical adduct **31** (Scheme 9) is trapped by a sulfur-centered radical scavenger. For this purpose, and yet applicable to activated and nonactivated alkenes, thiocyanates have recently evolved as useful reagents in combination with copper salts (*see* Chapter 6.04).[84,85] Alternatively, carbothiolation can be achieved with xanthates.[86,87]

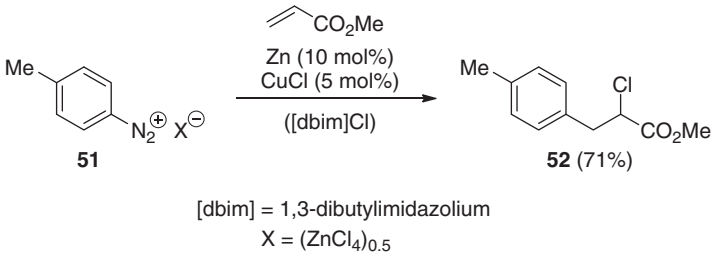
Carbohalogenation reactions are the classical versions of intermolecular Meerwein reactions.

Traditionally, copper halides are employed as sources for the halogen atoms, chlorine and bromine, in combination with aryl diazonium salts as aryl radical precursors. No examples have so far been reported for carbofluorinations involving aryl radicals, and as it will be shown below, carboiodinations are generally achieved by slightly modified procedures.

In the mechanisms of carbochlorination and carbobromination reactions, the copper salts usually play a double role.[88,89] In the oxidation state of copper(I), they lead to a reduction of the aryl diazonium salt, which liberates the aryl radical accompanied by a loss of nitrogen. In the oxidation state of copper(II), the salts are able to effectively deliver a chlorine or bromine atom to the adduct **31**. The halogenation step can hereby either occur through radical atom transfer or through the formation of an organocopper(III)-intermediate that undergoes reductive elimination.[90] Since the copper(II) salt is simultaneously reduced to a copper(I) salt, it can enter the catalytic cycle again. Due to the ability of chloride, bromide, and iodide ions to act as leaving groups, the carbohalogenation products may be further converted to the corresponding vinyl benzene derivatives through elimination of hydrogen chloride, -bromide, or -iodide (Scheme 9).

Activated alkenes, including styrenes, 1,3-dienes, acrylates, or vinyl ketones, have for a long time been the preferred substrates for Meerwein carbohalogenations.[11a] By using activated substrates, the addition step of the aryl radical to the alkene is sufficiently fast to compete with the direct halogen transfer leading to Sandmeyer products. Only a few examples are known for the functionalization of nonactivated alkenes.[84,91] Two particularly useful versions of the Meerwein carbohalogenation reactions have been developed by Doyle et al.[92] and Raucher and Koolpe[93]. Doyle's studies have shown that not necessarily aryl diazonium salts have to be used as aryl radical precursors, but that diazotization can also be achieved *in situ*. As a consequence, carbohalogenation products are also directly accessible from anilines and alkylnitrites in the presence of activated alkenes and copper salts. Raucher's work has led to an interesting application of the carbohalogenation reactions. By reacting 2-nitrophenyldiazonium salts with vinyl acetates and copper (II)-chloride, indoles can be prepared through just one further reductive step. Attempts to run Meerwein carbohalogenations enantioselectively by using chiral copper complexes for the halogen transfer have so far led to only low enantioselectivities.[94]

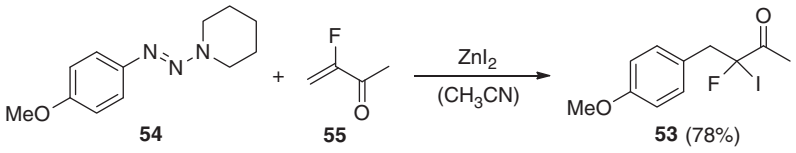
A modern version of the classical Meerwein reaction is depicted in Scheme 14.[95] By conducting the reaction of diazonium salt **51** with methyl acrylate in an ionic liquid, the copper catalyst loading could be reduced to amounts as low as 5 mol%. In addition, the yield of the products such as **52** became less sensitive to changes in the substitution pattern on the aryl diazonium salt.



Scheme 14 Meerwein carbohalogenation in ionic liquids.[95]

As mentioned before, carboiodination reactions have to be conducted under slightly modified conditions. Under classical conditions, and in the presence of copper ions, the iodine transfer to the aryl radical would otherwise be too rapid to allow the desired addition of the aryl radicals even to activated alkenes. A simple but effective solution is to use iodide ions in the absence of metal catalysts. Typically, the diazonium salt is hereby added to a mixture of potassium iodide and an activated alkene such as methyl acrylate.[96] In this way, the carboiodination takes advantage of the fact that aryl radicals are on the one hand readily generated through reduction with iodide, but on the other hand only slowly trapped by the iodide ion, which in turn enables addition reactions to alkenes.[2] As far as the iodine transfer to the alkyl radical adduct **31** (Scheme 9) is concerned, several iodine species have been proposed as radical scavengers.[97]

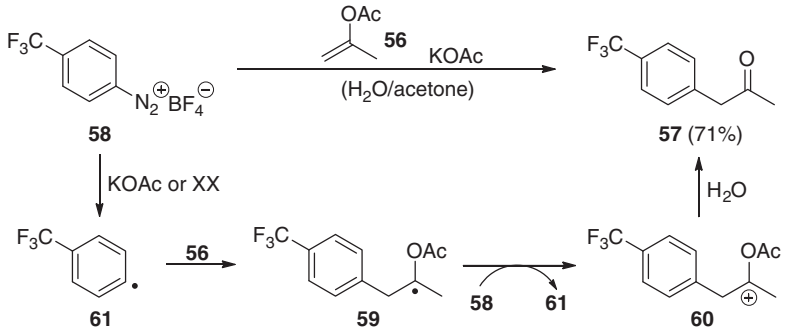
An example from a recently published study on Meerwein-type carboiodination reactions is shown in Scheme 15.[98] The reaction course leading to the fluoroiodoketone **53** can be rationalized by the above-mentioned general considerations. Interestingly, the diazonium salt has been exchanged for a triazene **54** as aryl radical source.[99] Since zinc does usually occur either as zinc(II) ion or elemental zinc(0), zinc(II)-iodide cannot act as an iodine atom transfer reagent comparable to copper(II)-iodide. The preferential use of zinc iodide instead of simple potassium iodide as halide source may be explained by its Lewis acidic character and therefore facilitated decomposition of the triazene.



Scheme 15 Carboiodination of 3-fluorobutenone (**55**).[98]

Reductive intermolecular Meerwein reactions, as shown at the beginning of this section, are characterized by the fact that the alkyl radical adduct **31** (Scheme 9) gets reduced to intermediates such as enolates. Depending on the nature of this adduct **31**, namely the type of substituents stabilizing the alkyl radical, it is also possible to further convert this intermediate into a cation by oxidation.

The type of alkenes used for this purpose are vinyl esters and vinyl ethers.[100] Aryl radical addition to these alkenes leads to electron-rich, nucleophilic alkyl radicals, which can be oxidized by an aryl diazonium salt or by another oxidant present in the reaction mixture. Given that the oxidation of the alkyl radical adduct initiates the generation of a new aryl radical, either directly through a reduction of a diazonium ion or indirectly via a redox catalyst, the radical arylation can be conducted as chain reaction. A recently published example for this reaction type is shown in Scheme 16.[101]



Scheme 16 Metal-free synthesis of arylmethyl ketones from aryl diazonium salts and isopropenyl acetate (**56**).[101]

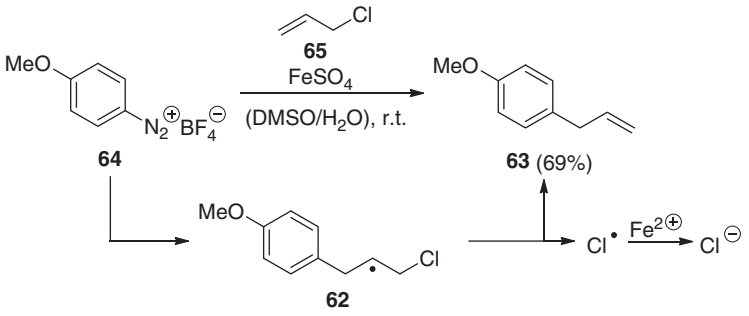
This methodology has been used to prepare benzyl methyl ketones **57** from diazonium salts **58** and isopropenyl acetate (**56**) under mild conditions. In the chain-propagating step, the nucleophilic radical **59** is oxidized to the cation **60**, whereas a new aryl radical **61** is generated from **58**.

Reactions, in which the chain propagation is achieved through the oxidation and reduction of a redox catalyst, have been developed recently by König and coworkers.[102] With a ruthenium-tris-2,2′-bipyridine complex or eosin Y as photocatalyst, and aryl diazonium salts as radical sources, a variety of styrenes could be efficiently converted to stilbene derivatives under simple irradiation. Noteworthy, this photocatalytic reaction is further applicable to phenylacetylenes. Comparable arylation reactions with iodo- and bromobenzenes mediated by potassium *tert*-butoxide and bathophen have been reported by Shi and coworkers.[103]

4.08.3.2.2 Addition-fragmentation reactions

Besides oxidation, reduction, and trapping by radical scavengers, the adducts **31** (Scheme 9) arising from the addition of an aryl radical to an alkene can also be further converted through a fragmentation step (*see* Chapter 6.19). Typical alkenes useful for this reaction type are allyl and vinyl chlorides and -bromides. Following an addition-fragmentation mechanism, allyl halogenides lead to a transfer of an allyl group in the so-called allylation reactions, and vinyl groups can be attached to arenes by suitable vinyl halogenides.

Although allyl bromides have for a long time been the preferred alkenes in allylation reactions,[104] due to a more rapid fragmentation of the bromine radical, recent studies have shown that allyl chlorides can give even better yields under suitable reaction conditions (Scheme 17).[105] Importantly, the chlorine radical liberated in the fragmentation step from **62** to **63** has to be rapidly reduced by additives such as iron(II)-sulfate to avoid side reactions. In the present example, iron(II)-sulfate also initiates the generation of aryl radicals from the diazonium salt **64**.



Scheme 17 Iron(II)-mediated radical allylation with allyl chloride (**65**).[105]

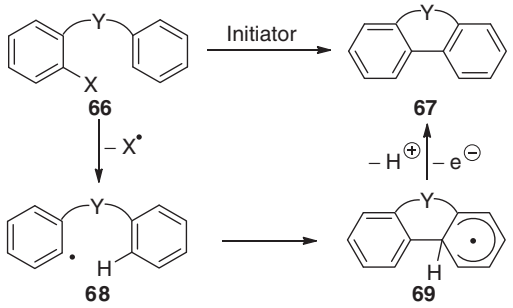
In short, radical vinylation reactions have also been applied in the synthesis of radiolabeled compound for positron emission tomography imaging.[106]

4.08.4 Substitution of Aromatics and Heteroaromatics through Aryl Radicals

4.08.4.1 Intramolecular Substitution – Pschorr-Type Cyclization Reactions

Comparable to intramolecular Meerwein reactions or cyclizations, most Pschorr reactions benefit from the close proximity of the reaction centers that is secured through suitable linkers between the two aromatic ring systems. For radical aryl–aryl coupling reactions,

the acceleration caused by the intramolecular reaction course is even more important than for aryl radical additions to alkenes since an aryl radical generally adds to an alkene at least 10 times faster than to a substituted benzene. It is therefore not surprising that the intramolecular Pschorr reaction[8] has been described in literature almost three decades before its intermolecular version, which is known as Gomberg–Bachmann reaction.[5] The common intermediates of Pschorr reactions are shown in Scheme 18.



Scheme 18 General mechanism of Pschorr reactions.

Common linker units between the two ring systems of **66** have a chain length of one or two atoms, so that five- or six-membered rings are formed in the cyclization to **67**. Heteroatoms frequently appear as linkers or parts of the chain. Depending on the structure of the linker and the substitution pattern of the two aromatic cores, the aryl radical attack may not only occur in *ortho*-position of the linker, as shown in Scheme 18, but also as an *ipso* attack at the carbon atom to which the linker is attached.

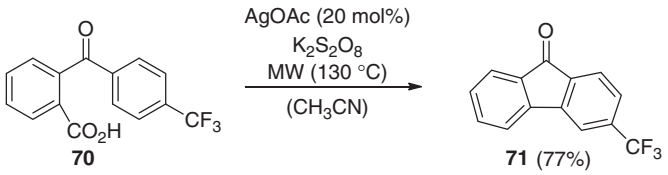
As the following examples will show, the generation of aryl radicals **68** in Pschorr reactions has largely shifted from the classical aryl diazonium salts to the use of halobenzenes as precursors. Although rearomatization represents the most common step in Pschorr reactions, several studies have demonstrated that the cyclized radical intermediate **69** can also be converted in other ways. Further details on the Pschorr reaction are summarized in several recent review articles.[6b,9,107]

4.08.4.1.1 Cyclization onto substituted benzenes

Cyclizations onto substituted benzenes, starting from aryl diazonium salts as radical precursors, represent the classical versions of the Pschorr reactions. The required aryl radicals have hereby been generated under photochemical and thermal conditions,[108] by electrochemical[97e] and metal-induced reduction,[109] by strong organic reductants[110] and by such simple additives as iodide ions (*see* Chapters 9.13 and 9.14).[111]

Interestingly, the cyclization of a stilbenediazonium ion into the corresponding phenanthrene using a tris-(2,2′-bipyridyl) ruthenium(II) complex as photoredox catalyst has already been reported by Cano-Yelo and Deronzier in 1980.[112] In the past years, ruthenium-based photocatalysts have been rediscovered and they are currently under intensive investigation in various fields of organic synthesis.

First attempts with carboxylic acids as aryl radical precursors in Pschorr reactions have been reported using electrochemical oxidation[113] or potassium peroxodisulfate.[114] These early procedures, which were focussed on the conversion of benzoylbenzoic acids into fluorenones, have now been significantly improved by Greaney and coworkers (Scheme 19).[115] By employing potassium peroxodisulfate in combination with catalytic amounts of silver acetate under microwave irradiation, benzoylbenzoic acid **70**, and several other substrates, could be cyclized to fluorenones such as **71**.

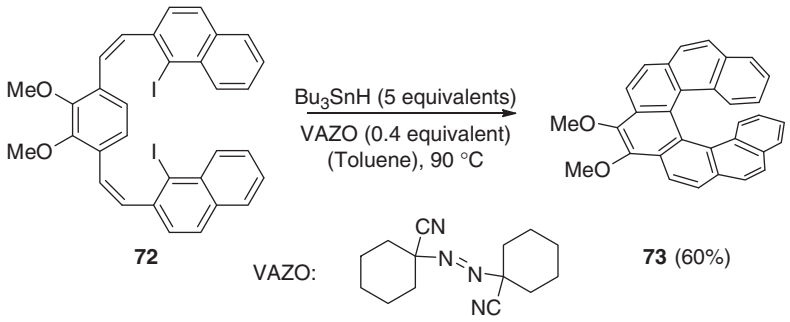


Scheme 19 Synthesis of fluorenones from benzoylbenzoic acids through a decarboxylative version of the Pschorr reaction.[115]

Recently, fluorenones have also been prepared from the boronic acid and trifluoroborate analogues of **70** using potassium peroxodisulfate and catalytic silver nitrate at lower temperatures of 60 °C.[116]

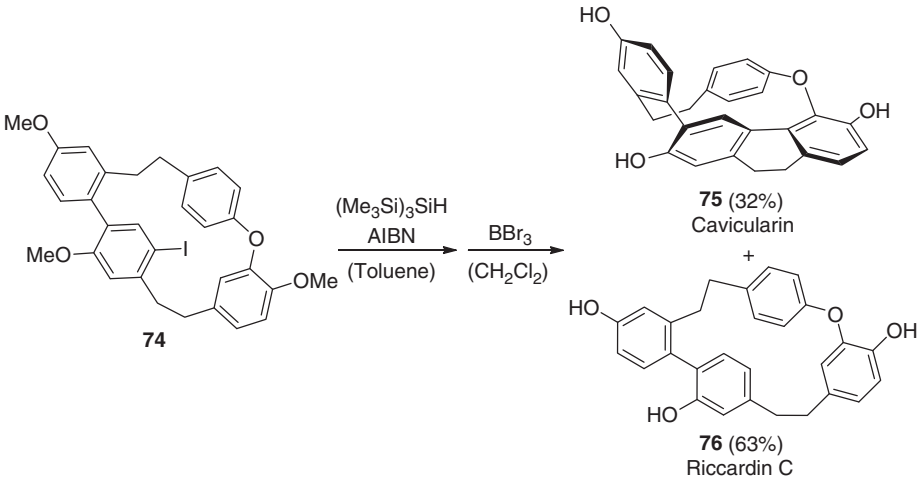
Regarding the Pschorr cyclizations which have been published over the past two decades, aryl iodides and aryl bromides have clearly become the most frequently used cyclization precursors. The most common reagent for the generation of aryl radicals in combination with these haloarenes certainly is tributyltin hydride.[117,118] A remarkable example featuring a twofold

tinhydride-mediated cyclization is shown in Scheme 20.[119] The effectiveness of the two intramolecular aryl radical addition steps, which are necessary to convert the diiodide **72** into the helicene **73**, becomes obvious from the fact that toluene could be used as solvent. In this context, the two (*Z*)-configured double bonds in **72** play a critical role, since their configuration pre-positions the reaction centers almost ideally for the cylizations.[120] In the case of an unfavorable (*E*)-stereochemistry and slow intramolecular addition steps, toluene would otherwise most likely stabilize the highly reactive aryl radical intermediates through hydrogen atom transfer from its benzylic positions. Due to this ability to function as hydrogen atom donor, toluene is generally not a recommended solvent for reactions proceeding via aryl radicals.[2]



Scheme 20 Synthesis of helicene **73** from diiodide **72** through a double Pschorr cyclization.[119]

In recent years, increasing efforts have been made to find replacements for organotin reagents that are less problematic with respect to toxicity and removal from reaction mixtures.[121] One of the most popular and widely used alternatives for tributyltin hydride that has emerged from these investigations is tris(trimethylsilyl)silane.[122] A beautiful example for a Pschorr reaction with this modern reductant is shown in Scheme 21.[123] Through an additional ring closure within the macrocyclic ether **74** and subsequent deprotection with boron tribromide, the natural product cavicularin (**75**) was obtained. The observation that riccardin C (**76**) was found as reduced and noncyclized byproduct of **74** in 63% yield could be explained by the use of the solvent toluene.



Scheme 21 A Pschorr reaction as a key step in the total synthesis of cavicularin (**75**).[123]

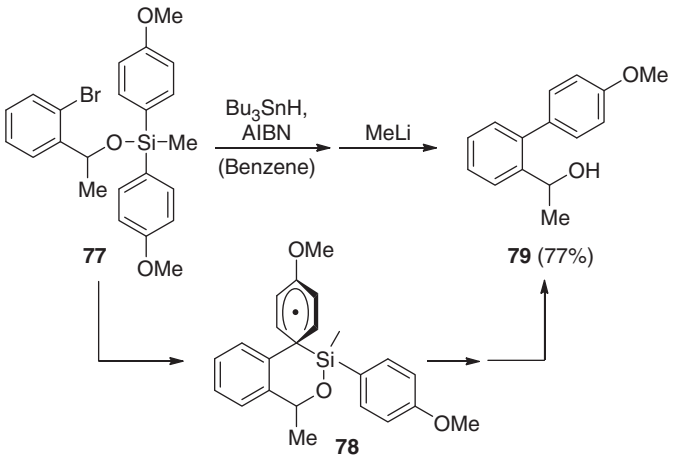
In Pschorr reactions of bromo- and iodoarenes with the stronger reductant samarium(II)-iodide different cyclization modes and reaction courses could be observed, namely the further reduction of the cyclohexadienyl intermediate **69** (Scheme 18) to a cyclohexadiene.[124] Moreover, Pschorr reactions of 2-bromobenzophenones to fluorenones have recently been conducted under photochemical initiation.[125]

Heteroarenes can be significantly more reactive toward aryl radicals than substituted benzenes, but the rearomatization step following the aryl radical attack is then often also more difficult to achieve. In intramolecular Pschorr-type reactions, imidazoles[126] and pyridines[120,127] have recently been used as aryl radical acceptors.

4.08.4.1.2 Intramolecular addition – ipso substitutions

Depending on the substitution pattern of the arene, acting as radical acceptor and the length of the spacer unit between the two aromatic systems, *ipso* substitutions can occur as preferred mechanistic pathway of the Pschorr reaction. With regard to the further fate of the radical adducts arising from the *ipso* attack, two main areas of synthetic applications have emerged in recent years.

Given that the *ipso* attack is followed by rearomatization through a fragmentation step, the Pschorr reaction can become a useful tool for biaryl synthesis. A representative example is shown in Scheme 22.[128]



Scheme 22 Synthesis of biphenyl **79** through an intramolecular *ipso* substitution.[128]

Regarding the reactant **77** and the corresponding aryl radical, the *ipso* attack leading to **78** is certainly favored by the length of the linker between the two aromatic systems (three atoms). Shorter linkers do also allow an aryl attack in *ortho*-position to the silyloxy substituent. Fragmentation of **78** leads to a stabilized silicon-centered radical which is further reduced. Desilylation with methyl lithium finally gives the biphenyl alcohol **79**.[129] Pschorr-type reactions proceeding via an *ipso* attack with subsequent fragmentation have also been reported for sulfonamides, sulfonates,[130] azetidinones,[131] and phosphinates[132] acting as linkers for the two aromatic systems. Generally, this type of biaryl synthesis represents a very useful tool to circumvent the two basic difficulties of intermolecular radical substitutions of arenes, which are slow radical addition steps (leading to side reactions) and usually low regioselectivity.

In case that the intramolecular *ipso* attack is not followed by a fragmentation step leading to rearomatization, Pschorr reactions can be employed for the synthesis of spirocyclic systems.

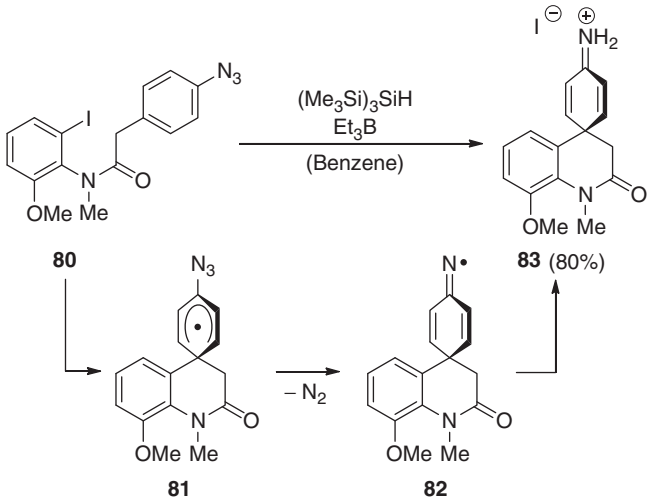
Since the cyclohexadienyl radical adduct must then be further converted through some other type of fragmentation reaction, the nature of the substituent in *para*-position relative to the attacked carbon atom, plays a critical role.

One particular group of substituted benzenes, that is well suited as aryl radical acceptor with regard to these requirements are phenyl azides.[133] As shown in Scheme 23, the intramolecular attack of the aryl radical generated from **80** by tris(trimethylsilyl) silane leads to the cyclohexadienyl intermediate **81**. Fragmentation through a homolytic bond cleavage at the *ipso*-position is now no longer the preferred pathway (cf. Scheme 22), since the radical **81** can stabilize via a loss of nitrogen from the azide functionality (*see* Chapter 1.02). The iminyl radical **82** is then further reduced and finally protonated to give the spirocyclic iminium salt **83**.

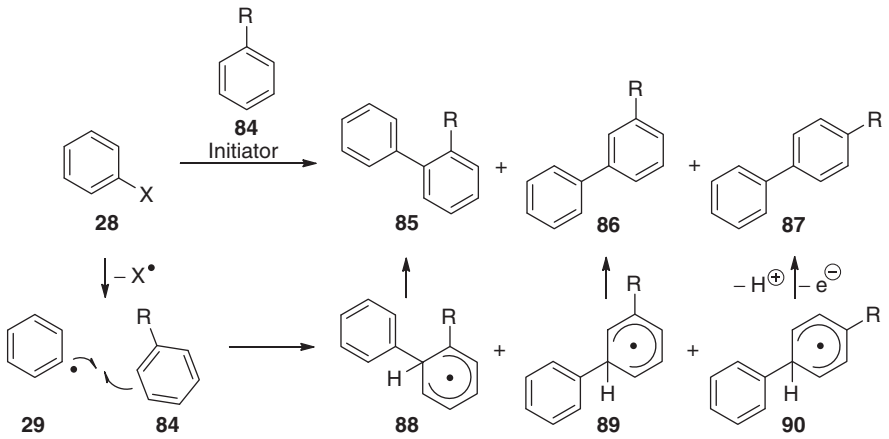
Comparable spirocyclizations of phenyl silyl ethers as aryl radical acceptors have been reported by De Turiso and Curran.[134] In these reactions the spirocyclic radical adduct stabilizes through a homolytic cleavage of the silicon–oxygen bond of the ether to liberate a stabilized silyl radical. Moreover, the spirocyclic adducts can undergo rearrangements leading to biphenyls. Photocatalyzed reactions of this type have been developed by Charette and coworkers.[135]

4.08.4.2 Intermolecular Substitution – Gomberg–Bachmann Reactions

Among all the reaction types discussed so far, Gomberg–Bachmann reactions are the most difficult to conduct with regard to kinetics and regioselectivity (Scheme 24). As it will be shown in this section, a variety of aryl radical precursors **28** can be used for intermolecular arylation reactions. The first general difficulty arises in the following step, since the addition of aryl radical **29** to substituted benzenes **84** is a comparatively slow process ($k \sim 10^6\ M^{-1}\ s^{-1}$) in relation to possible side reactions of the aryl radical, such as hydrogen abstraction.[2,12] Moreover, only very few substituents R are able to exert a remarkable control on the aryl radical attack so that useful regioselectivities can be achieved. From most Gomberg–Bachmann reaction with aryl radical acceptors other



Scheme 23 Synthesis of spirocyclic compounds through a Pschorr reaction proceeding via an *ipso* attack.[133]



Scheme 24 Intermolecular radical substitution of benzene derivatives.

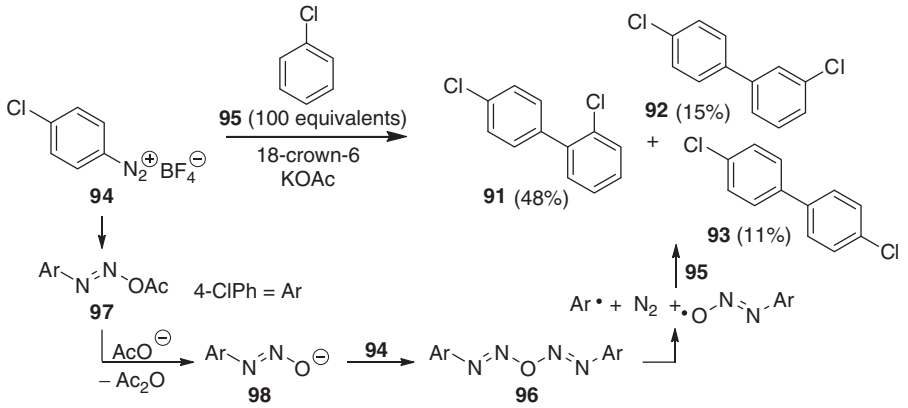
than benzene (or suitable symmetrically substituted benzenes) more or less complex product mixtures of *ortho*-, *meta*-, and *para*-substituted biphenyls **85**, **86**, and **87** are obtained.

The final rearomatization step from the radical cyclohexadienyl intermediates **88**–**90** to the biphenyls **85**–**87** does usually proceed without complications. As mentioned before, the final rearomatization can more easily be circumvented when heteroarenes are employed as aryl radical acceptors instead of substituted benzenes. In the presence of very efficient hydrogen atom transfer reagents, such as phenylselenol, arenes as well as heteroarenes can be dearomatized through radical addition and further reduction of the cyclohexadienyl intermediate. Various examples for such reductive radical arylations have been reported by Crich et al.[136]

4.08.4.2.1 Substitution of benzene and substituted benzenes

Due to no regioselectivity issue, benzene has always been by far the most popular aryl radical acceptor in Gomberg–Bachmann reactions.[6a,137] Furthermore, benzene can easily be applied in large excess, usually as solvent, which effectively counterbalances the comparably slow aryl radical addition step.[7] In classical Gomberg–Bachmann reactions, aryl diazonium salts are used as aryl radical precursors. According to the mechanistic investigations by Rüchardt and Merz,[138] the generation of the aryl radical is promoted by the presence of a base, which converts the diazonium salt into highly reactive diazoanhydrides. The homolytic cleavage of the diazoanhydrides then results in the liberation of the aryl radicals.

A biphenyl synthesis that has been conducted according to an improved protocol for Gomberg–Bachmann reactions is shown in Scheme 25 together with more mechanistic details.[139] Under phase-transfer conditions (5 mol% of crown ether and 2 equivalents of potassium acetate), a mixture of dichlorobiphenyls **91**–**93** is obtained from 4-chlorophenyldiazonium

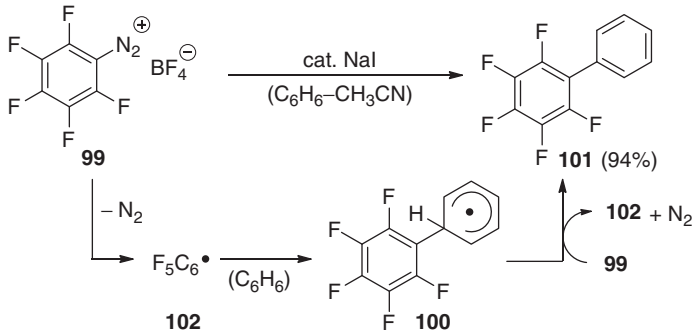


Scheme 25 Synthesis of dichlorobiphenyls through a phase-transfer Gomberg–Bachmann (PTGB) reaction.[139]

tetrafluoroborate (**94**) and chlorobenzene (**95**). As it is typical for Gomberg–Bachmann reactions the aryl radical acceptor chlorobenzene **95** has been used as solvent in nearly 100-fold excess over the diazonium salt **94**.

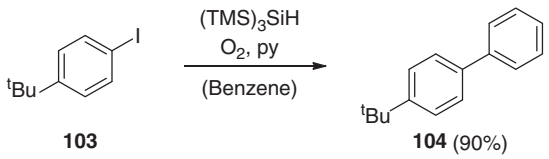
The key intermediates of the reaction mechanism are reactive diazoanhydrides **96**, which are formed from the diazonium ions via phenyldiazonium acetates **97** and phenyldiazotates **98**. Homolytic decomposition of **96** produces the required aryl radical, nitrogen, and a phenyldiazoxyl radical that might be able to promote the rearomatization step through hydrogen abstraction from the cyclohexadienyl intermediates.

Given that strongly oxidizing aryl diazonium salts such as **99** are employed as reactants, no base is necessary and the radical arylation can be conducted as a chain reaction (Scheme 26).[140] The key step propagating the radical chain is the oxidative rearomatization of **100** to **101**, in which the diazonium ion **99** is simultaneously reduced and thus a new aryl radical **102** is formed.



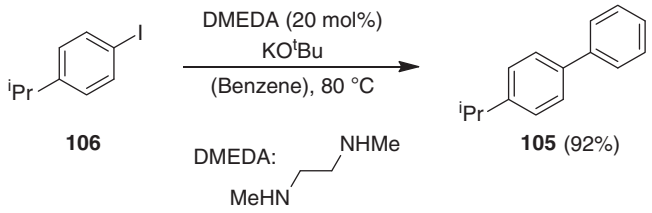
Scheme 26 Radical arylation of benzene with a pentafluorophenyl diazonium salt.[140]

Interestingly, comparable chain reactions are also observed when only moderately reactive aryl diazonium salts are combined with extremely electron-rich arenes, such as phenylene-diamine.[141] Concerning the rearomatization of the radical cyclohexadienyl intermediate, it has recently been shown that oxygen is a very effective reagent to promote this step.[142] An example from the related study is depicted in Scheme 27. As an alternative to aryl diazonium salts, the aryl radicals have been generated from iodobenzenes, such as **103**, through reduction with tris(trimethylsilyl)silane to give biphenyls **104** in high yields.



Scheme 27 Tris(trimethylsilyl)silane-mediated synthesis of biphenyls from iodobenzenes in the presence of oxygen.[142]

Tris(trimethylsilyl)silane is also a useful reagent to achieve Gomberg–Bachmann reactions of heteroarenes.[143] Very recently, even more simple conditions have been discovered for the generation of aryl radicals from iodobenzenes. As a pioneer in this field, Itami and coworkers[144] found that potassium *tert*-butoxide alone can promote the formation of biaryls from iodo- or bromobenzene with electron-efficient heterocycles such as pyridine, pyridazine, pyrimidine, and pyrazine. Since none of the desired biaryl products were observed in control experiments with radical trapping reagents like TEMPO or acrylonitrile, a radical reaction mechanism appears plausible. An extension of the substrate scope to benzene and substituted benzenes as aryl radical acceptors is possible when *tert*-butoxides are used in combination with ligands such as phen or *N*,*N*′-dimethyl-ethylene diamine (DMEDA) to generate aryl radicals from bromo- and iodobenzenes.[145–147] A representative example for this type of organocatalytic biaryl synthesis is shown in Scheme 28.[147]



Scheme 28 Organocatalytic synthesis of biphenyls.[147]

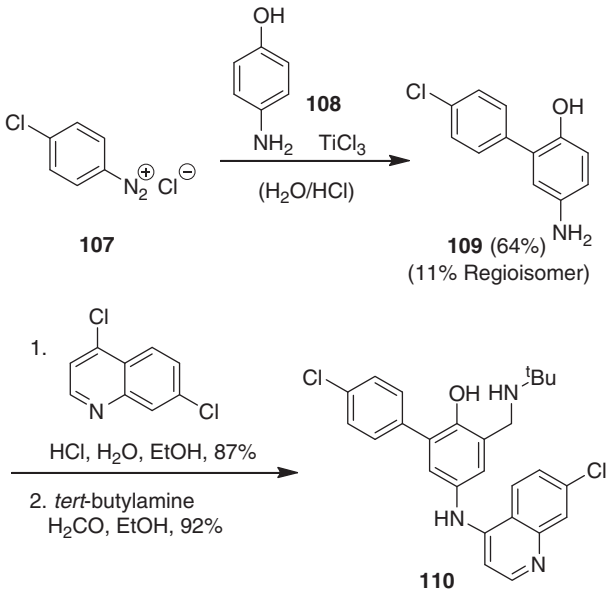
Again, the addition of TEMPO led to a complete suppression of the formation of biphenyl **105** from iodobenzene **106**, which points to radical intermediates. A more detailed discussion of possible reaction mechanisms for these base-promoted homolytic aromatic substitutions has shortly been published by Studer and Curran.[148]

New sources for aryl radicals that have found application in Gomberg–Bachmann-type reactions are aryl boronic acids and aryl hydrazines in the presence of manganese(III)-acetate,[149,150] as well as aryl hydrazines in combination with potassium permanganate.[151] The oxidative generation of aryl radicals from aryl hydrazines generally proceeds via phenyldiazenes,[152] which further decompose under loss of nitrogen. At elevated temperatures in refluxing chlorobenzene no special oxidant is necessary since aryl hydrazines are oxidized by the oxygen from air. This methodology was applied for the arylation of fullerenes.[153] Gomberg–Bachmann reactions with 2-aminophenyl radicals, which are available from benzotriazols under irradiation, have also recently been reported.[154]

Besides the investigation of new precursors for aryl radicals and the development of suitable reaction conditions for those reagents, the Gomberg–Bachmann reaction has also been extended to new aryl radical acceptors. The efforts with new substrates are aimed at a broader range of products and at reactions proceeding with higher regioselectivity. Compared to the radical phenylation of fluorobenzene and benzonitrile leading to *ortho*-, *meta*-, and *para*-products in ratios of 59:31:10 and 60:14:26, respectively, good regioselectivities are observed under the same phase-transfer conditions (cf. Scheme 25) for the phenylation of anisole (*ortho*:*meta*:*para* = 91:2:7).[139] Phenol, which could lead to a comparably favorable product distribution as anisole due to its electron-donating substituent, cannot be converted under classical Gomberg–Bachmann reaction conditions. The basic conditions would lead to deprotonation and azo coupling with the diazonium ions. Under acidic conditions, in contrast, phenols have been found to be useful reactants in radical arylation reactions.[155] An example from a recent report on the synthesis of biphenyls from substituted phenols is depicted in Scheme 29.[141]

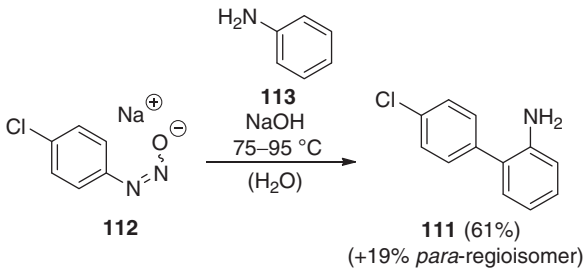
In the related studies, titanium(III)-chloride turned out to be an especially useful reagent to generate aryl radicals from arenediazonium salts under acidic conditions.[156] Although only a moderate regioselectivity could finally be achieved in the reaction of the diazonium salt **107** and 4-anisidine (**108**), the value of the radical arylation becomes obvious from the fact that the alterative organometallic access to biphenyl **109**, which is precursor of the antimalarial tebuquine (**110**), comprises five steps including necessary protection and deprotection.[157] Titanium-mediated radical arylation reactions of phenols were recently further applied in the syntheses of BACE inhibitors[158] and neurotensin receptor ligands.[159]

As mentioned above, phenolates are incompatible to radical reactions with aryl diazonium salts due to the preferred formation of azo compounds. If the diazonium salts are replaced by phenylazosulfides as a sort of protected diazonium ions, the radical arylation of phenolates becomes possible. Pioneering work in this field has been reported by Petrillo et al.[160] The azosulfides hereby react with the phenolates under photochemical initiation according to a $S_{RN}1$ mechanism.[14] One group of substituted benzenes that has for a long time not at all appeared as aryl radical acceptor in Gomberg–Bachmann reactions are anilines. In combination with diazonium salts, and under neutral or basic conditions, azo coupling and triazene formation are most likely to occur as side reactions. The first types of protected diazonium ions that have recently been reported to be applicable for the arylation of anilines are azocarboxylates.[83] More easily accessible protected derivatives of diazonium ions, that are also suitable for aniline arylation, are their corresponding diazotates.[161] Phenyldiazotates **98** (cf. Scheme 25) are known to occur in Gomberg–Bachmann reactions as intermediates in the stepwise transformation of diazonium ions to diazoanhydrides **96**. In contrast to the diazoanhydrides **96**, diazotates **98** appear to be far better protected against ionic side reactions with anilines. This advantage of diazotates over diazoanhydrides can be exploited by simply conducting Gomberg–Bachmann reactions under strongly basic



Scheme 29 Synthesis of the antimalarial tebuquine (**110**) employing a radical arylation as key step.[141]

conditions, which make the better nucleophile-resistant diazotates to occur as main intermediates. A representative example from the related study is depicted in Scheme 30.



Scheme 30 Arylation of anilines with aryl diazotate under strong basic conditions.[161]

2-Aminobiphenyls such as **111**, which is readily accessible from diazotate **112** and aniline **113**, play an important role in the industrial synthesis of fungicides. It is interesting to note that the arylation of several *para*-substituted anilines under identical conditions led to a remarkable *ortho*:*meta*-selectivity of greater than 20:1. The amino functionality in anilines therefore appears to be a highly directing substituent in radical arylations.

Quinones are known as suitable acceptors for aryl radicals. Recently, the corresponding arylation reactions could be simplified in the way that anilines can be directly employed as radical precursors through the use of *tert*-butyl nitrite.[162] The new methodology is thus comparable to the variant of the Meerwein reaction developed by Doyle et al.[92] Furthermore, the radical arylation of benzoquinones has shortly been achieved with aryl boronic acid under oxidative conditions.[163]

Several heteroarenes represent better aryl radical scavengers than substituted benzenes. One especially reactive heterocyclic acceptor is furan. Studies with substituted furans have recently revealed a remarkable dependence of the chemoselectivity in radical arylation reactions on the hydrophilicity of the aryl radical.[164] Related to the tris-(2,2′-bipyridyl)ruthenium(II)-catalyzed Pschorr cyclization reported by Cano-Yelo and Deronzier,[112] König and coworkers have now achieved the intermolecular arylation of furan and other heterocycles with aryl diazonium salts under photoredox catalysis.[165]

4.08.5 Aryl Radicals in Carbon–Heteroatom Bond Formation

A large variety of carbon–heteroatom bond formations can be achieved by reacting aryl radicals with nucleophiles under $S_{RN}1$ reaction conditions. These reaction types have comprehensively been reviewed by Norris[166] and Rossi et al.[14] and comprise C–N, C–P, C–As, C–Sb as well as C–O, C–S, C–Se, and C–Te bond formations.

Alternatively, carbon–heteroatom bonds can be formed in reactions which are mechanistically more closely related to the classical Sandmeyer and Meerwein reactions. Various functionalized aryl boronates have very recently been prepared through either copper(I)-catalyzed reactions of aryl diazonium salts[167] or by metal-free processes from anilines which involves intermediate diazotization with *tert*-butyl nitrite.[168] Carbon–nitrogen bond formation is readily achieved by the addition of aryl radicals to the nitrogen atom of suitable imines[61] or to the N–N double bond of azo compounds.[169] Amination reactions with imines as aryl radical acceptors are useful tools for the synthesis of indolines.[170] Radical phosphination reactions of arenes can be conducted by using the corresponding iodoarenes and chlorophosphines as starting materials in the presence of tris(trimethylsilyl)silane.[171]

Several early examples have been reported for the formation of carbon–oxygen bonds through reactions proceeding via aryl radicals, either under metal-free conditions or with copper catalysis.[172] Recent developments include the use of oxygen in combination with phenylazocarboxylates.[83] Several strategies also exist for the introduction of sulfur atoms as substituents on the aromatic core. The classical Sandmeyer reactions can be conducted in the presence of anions such as thiocyanate,[173] or azosulfides can be irradiated to give thioethers under loss of nitrogen.[174] When Meerwein reactions are run under an atmosphere of sulfur dioxide, the aryl radical is converted to a sulfonyl radical before addition to the alkene.[175] In this way, a variety of alkyl–aryl sulfones can be obtained as reaction products. The classical Sandmeyer reaction,[2] which traditionally aims at the formation of carbon–halogen bonds, has also continuously improved with regard to substrate scope and catalyst effectivity.[173]

4.08.6 Summary

Meerwein, Pschorr, and Gomberg–Bachmann reactions are widely known transformations proceeding via aryl radicals. Due to their discovery in the early decades of the twentieth century, or as in case of the Pschorr reaction even before 1900, all of these reaction types have gone through a long history of developments and improvements. Although aryl diazonium ions were at first by far the most widely used source for aryl radicals, bromo- and iodobenzenes have been gaining more and more importance since the 1980s. Recent studies showing that organotin compounds can be well replaced by nontoxic reagents have further increased the attractiveness of aryl radical generation from haloarenes. Aryl boronic acids have been newly discovered as sources for aryl radicals and diazonium ions and hydrazines have been going through a remarkable revival in the past years. Given the number of different aryl radical precursors available together with the new insight on how to achieve selectivity in radical arylations, the classic aryl radical reaction types are becoming more and more widely applicable as well as increasingly attractive tools in organic synthesis.

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4.09 Nucleophilic Coupling with Arynes

H Yoshida, Hiroshima University, Higashi-Hiroshima, Japan

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Glossary

Bisaryne A compound having two arynic triple bonds.

Corannulyne A compound having an arynic triple bond in an outer rim of corannulene.

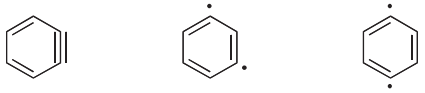
Heteroaryne A compound having an arynic triple bond in a heteroaromatic skeleton.

Nucleofugacity Leaving ability.

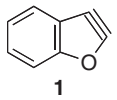
Trisaryne A compound having three arynic triple bonds.

4.09.1 Introduction

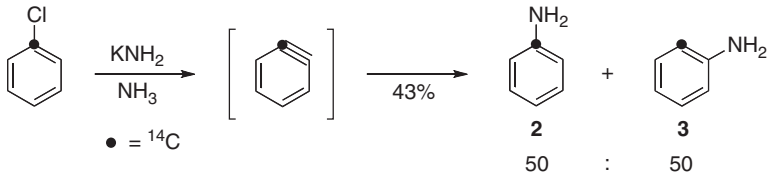
Arynes are neutral reactive intermediates, which have didehydroaromatic systems as common structures. Their simplest prototype is generally called benzyne (C_6H_4), and the species consists of three isomers, that is, *ortho*-, *meta*-, and *para*-benzyne.[1] Because this chapter deals with the advances in synthetic application of nucleophilic coupling with *ortho*-benzyne and its derivatives bearing a formal carbon–carbon triple bond, the term 'aryne' herein refers to them definitely.



Although Stoermer and Kahlert first speculated, as early as 1902, the intermediacy of an aryne (2,3-didehydrobenzofuran **1**) in the *cine*-substitution of 3-bromobenzofuran by an ethoxy moiety,[2] it took approximately 50 years before Roberts et al. decisively demonstrated the existence of the intermediate by the reaction of ^{14}C-labeled chlorobenzene with potassium amide, which afforded equal amounts of anilines **2** and **3** (equation 1).[3] Further evidence for its involvement in the reaction with phenyllithium or the Diels–Alder reaction with furan was reported shortly afterwards by Huisgen and Rist[4] or Wittig,[5] respectively.[6]



1



(1)

The most important structural feature of arynes is bending in the triple bond, which leads to an efficient mixing of the π^* orbital with the σ^* orbital and lowering the lowest unoccupied molecular orbital energy level considerably (Figure 1).[7] Hence, arynes exhibit salient electrophilicity, being completely opposite to the nucleophilic character of alkynes, and much attention has been paid to the coupling reactions of arynes with various nucleophiles. Because the aim of this chapter is to update the progress on the nucleophilic coupling with arynes since the publication in 1991 of *Comprehensive Organic Synthesis (COS)*,[8] the references used are mainly those published in 1990–2011. Detailed history of arynes, their structural analysis based on spectra and theoretical calculation, and earlier literatures have been discussed in *COS* (1991) and other excellent reviews.[9–27]

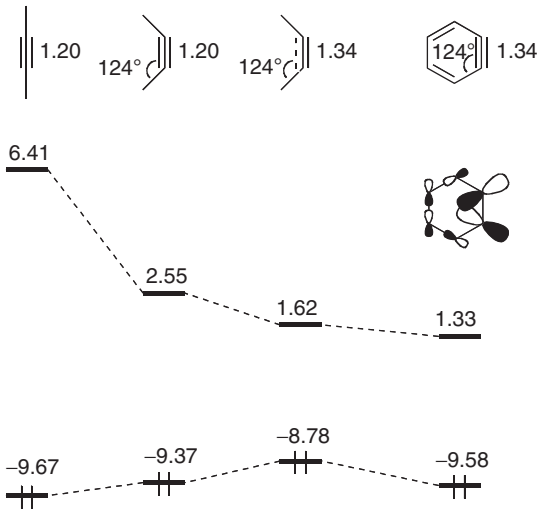


Figure 1 Frontier orbitals and energies (eV) for 2-butyne models and benzyne.

Although arynes are also well known to undergo transition metal-catalyzed reactions and pericyclic reactions such as [4 + 2] cycloaddition (Diels–Alder reaction), [3 + 2] cycloaddition (1,3-dipolar cycloaddition), and ene reaction,[13,18,20,21,23] this chapter does not basically include these reactions with the exception of [2 + 2] cycloaddition, in which the electrophilic character of arynes governs the progress.

4.09.2 Generation of Arynes

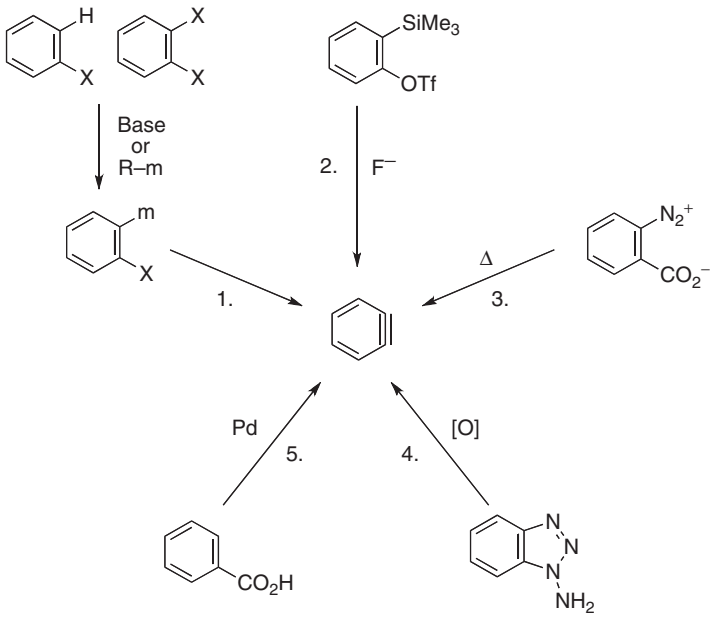
Owing to the high reactivity and transiency, arynes must be generated *in situ* by use of suitable precursors, and many methods for the generation, which can be classified into five categories, have hitherto been developed: (1) deprotonation and halogen–metal exchange, (2) carbon–silicon bond cleavage, (3) thermolysis, (4) oxidation, and (5) transition metal-catalyzed decarboxylation (Scheme 1). Since efficiency of the reactions using arynes is often dependent on the generation methods, we have to deliberate over the reaction modes, functional group compatibility of the methods, and availability of the precursors.

4.09.2.1 Deprotonation and Halogen–Metal Exchange

Aryl anions bearing such a good leaving group as halogen, OTf, or OTs in the *ortho*-position facilely undergo β-elimination to afford arynes, and the formation of the aryl anions can usually be achieved by deprotonation and halogen–metal exchange.

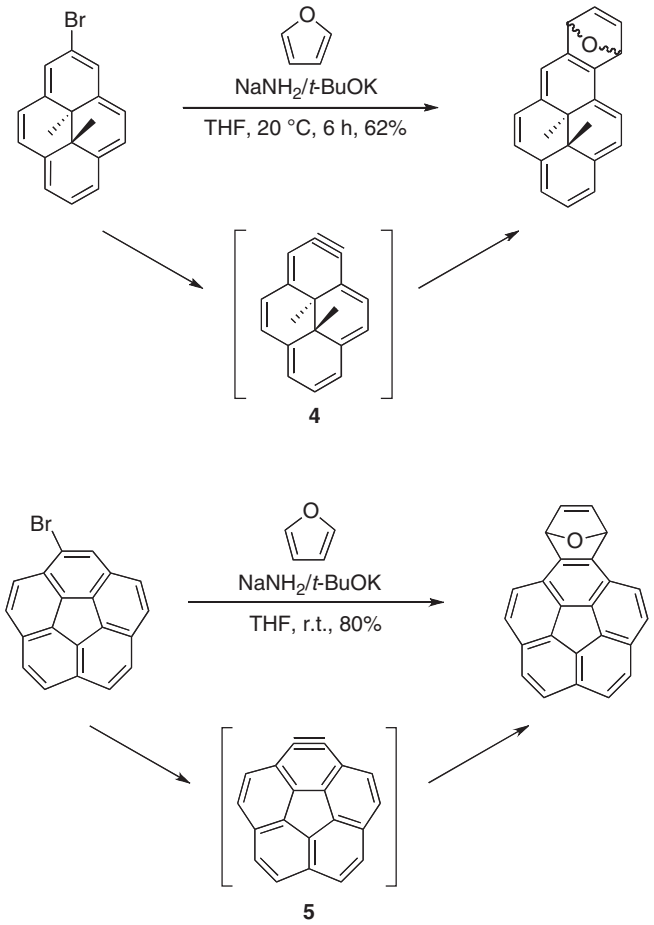
4.09.2.1.1 Deprotonation

The major advantage of the deprotonation process, being the oldest and simplest method for the generation of arynes, over other procedures is that it requires only monosubstituted aryl halides (or pseudohalides) of high availability, and thus even macrocyclic



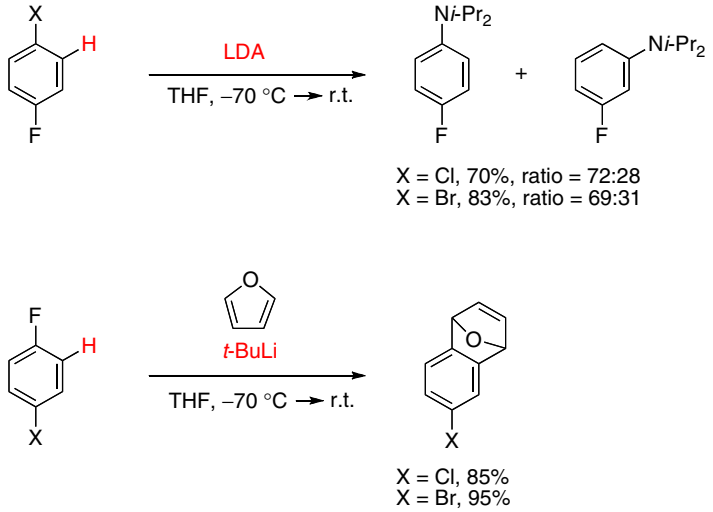
Scheme 1

arynes, [14] annulyne **4**,[28] and corannulyne **5**,[29] can be efficiently generated by treatment of the respective aryl bromides with $NaNH_2$/*tert*-BuOK (Scheme 2).



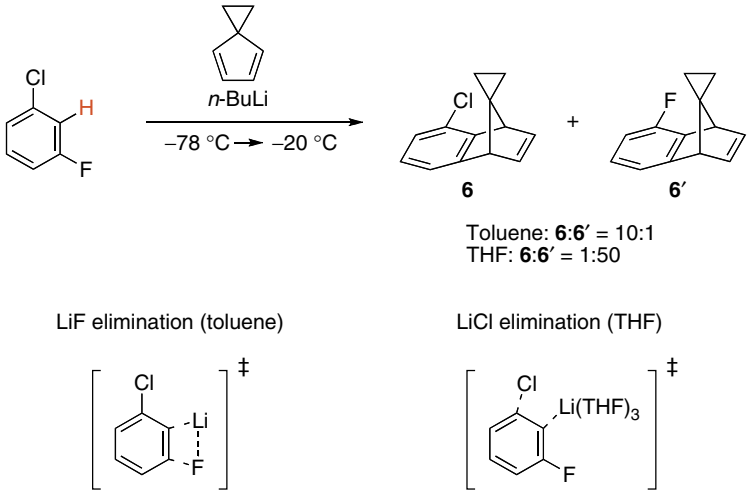
Scheme 2

As relative nucleofugacity of halide is I > Br > Cl > F but relative rates of deprotonation (*ortho* H to X) are in the reverse order, and furthermore the deprotonation step is basically reversible, regioselectivity in the formation of arynes from dihaloarenes possessing different halogens is governed by bases and reagents. For example, 1-fluoro-4-halobenzenes react with lithium diisopropyl amide (LDA) to give solely fluoro-*N*,*N*-diisopropylanilines by the loss of a halide of greater nucleofugacity, whereas the reaction with furan using *tert*-BuLi provides the cycloadducts through the selective release of a fluoride ion (**Scheme 3**).[30]

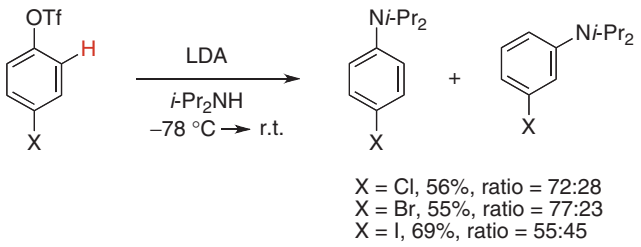


Scheme 3

In addition, elimination of a halide is also affected by solvents: treatment of 1-chloro-3-fluorobenzene with spiro[2.4]hepta-4,6-diene and *n*-BuLi in toluene affords **6** as the major product, but in marked contrast, opposite regioselectivity is observed by use of tetrahydrofuran (THF).[31,32] As depicted in **Scheme 4**, highly stabilizing Li–F interaction, which facilitates LiF elimination, is pronounced in toluene of less coordinating ability, whereas selective release of a chloride ion of higher nucleofugacity is ascribable to solvation with THF.[33] It should be noted that OTf group is apt to be eliminated relative to any of halides (equation 2).[34]

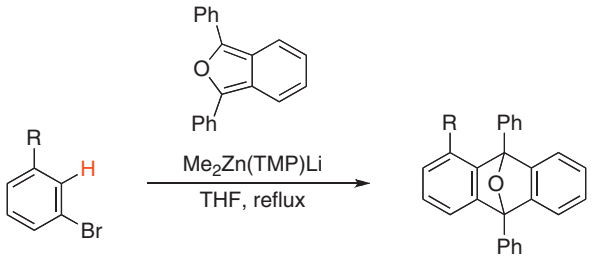


Scheme 4



(2)

The use of TMP-zincate, $Me_2Zn(TMP)Li$, as a base enables generation of arynes bearing electrophilic substituents (CN, CON*i*-Pr_2, and CO_2*t*-Bu),[35,36] which would be otherwise difficult to be formed with conventional strong bases (equation 3). Although $(SR_2)^+$[37–39] and $(SeR_2)^+$[40] also serve as a leaving group, the methods are of little advantage over those with halides or triflates.

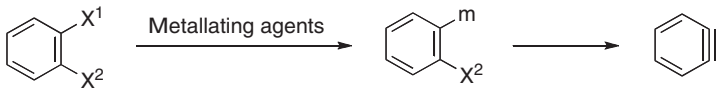


R = CN, 90%
R = CON*i*-Pr_2, 100%
R = CO_2*t*-Bu, 88%

(3)

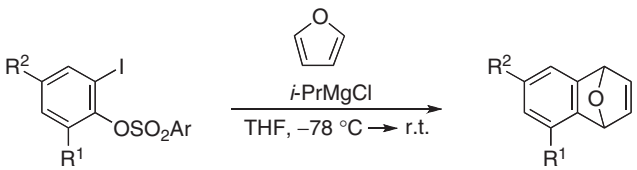
4.09.2.1.2 Halogen–metal exchange

The halogen–metal exchange of *ortho*-dihaloarenes is also the common and reliable way of generating arynes[41–48] and is applicable to various 2-haloaryl sulfonates (triflate, tosylate, 4-chlorophenylsulfonate, etc.) that are directly accessible from 2-halophenols (Scheme 5).[49–53] Owing to highly basic reaction conditions, the halogen–metal exchange with traditional metallating agents such as *n*-BuLi and Mg often prevents the use of aryne precursors having base-sensitive functional groups; however, the functional group compatibility has been significantly improved by employing *i*-PrMgCl (or *i*-PrMgCl · LiCl)[51,54,55] or Me_3ZnLi,[35,36] where allyl, Bz, CO_2Me, I, etc. are tolerated throughout the reactions (Scheme 6). Lanthanum metal[56,57] and stannyl anionic species derived from $Me_3SiSnBu_3$ and a fluoride ion[58,59] serve as the metallating agents of *ortho*-dihaloarenes as well (Scheme 7).

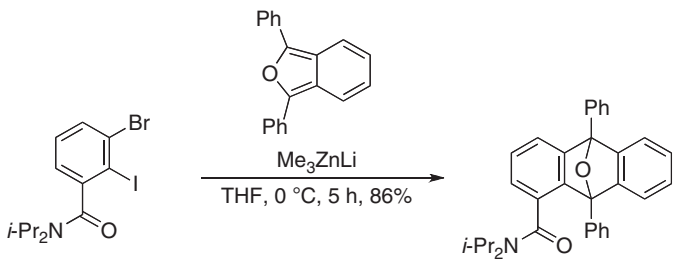


X^1 = Br, I
X^2 = halogen, OTf, OTs, $OSO_2(4\text{-}ClC_6H_4)$, etc.
m: Li, Mg, Zn, etc.

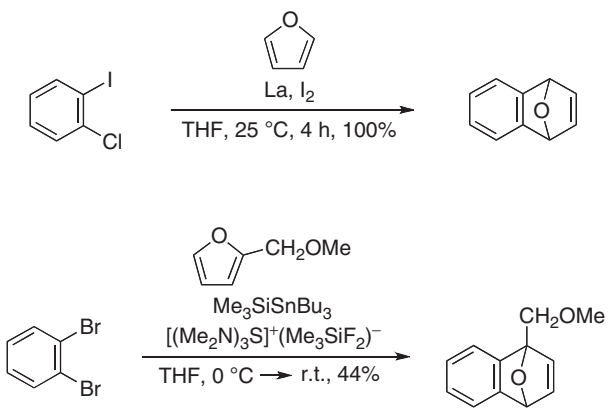
Scheme 5



R^1 = H, R^2 = CO_2Me, 93%
R^1 = allyl, R^2 = I, 88%
R^1 = Bz, R^2 = I, 68%



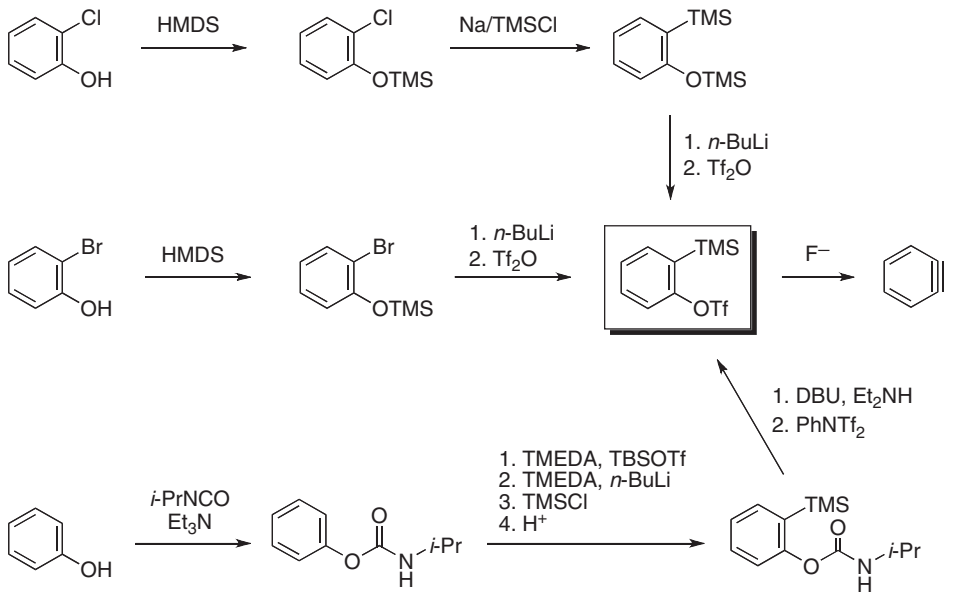
Scheme 6



Scheme 7

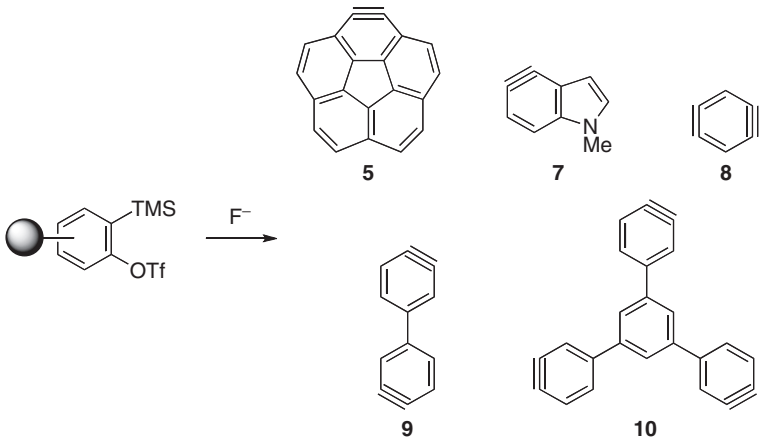
4.09.2.2 Carbon–Silicon Bond Cleavage

The facility of aryl–silicon bond cleavage by a fluoride ion (or by an alkoxide occasionally) allows the utilization of arylsilanes possessing an *ortho* leaving group as aryne precursors.[60,61] In particular, the combination of 2-(trimethylsilyl)aryl triflates, being readily available from phenols or 2-halophenols (Scheme 8),[62–65] with a fluoride ion has been the mainstay for remarkable progress in organic synthesis using arynes in the past decade because the generation of arynes takes place efficaciously even at room temperature (cryogenic and elevated temperature is unnecessary) under neutral conditions, which expands the versatility of the reactions of arynes.

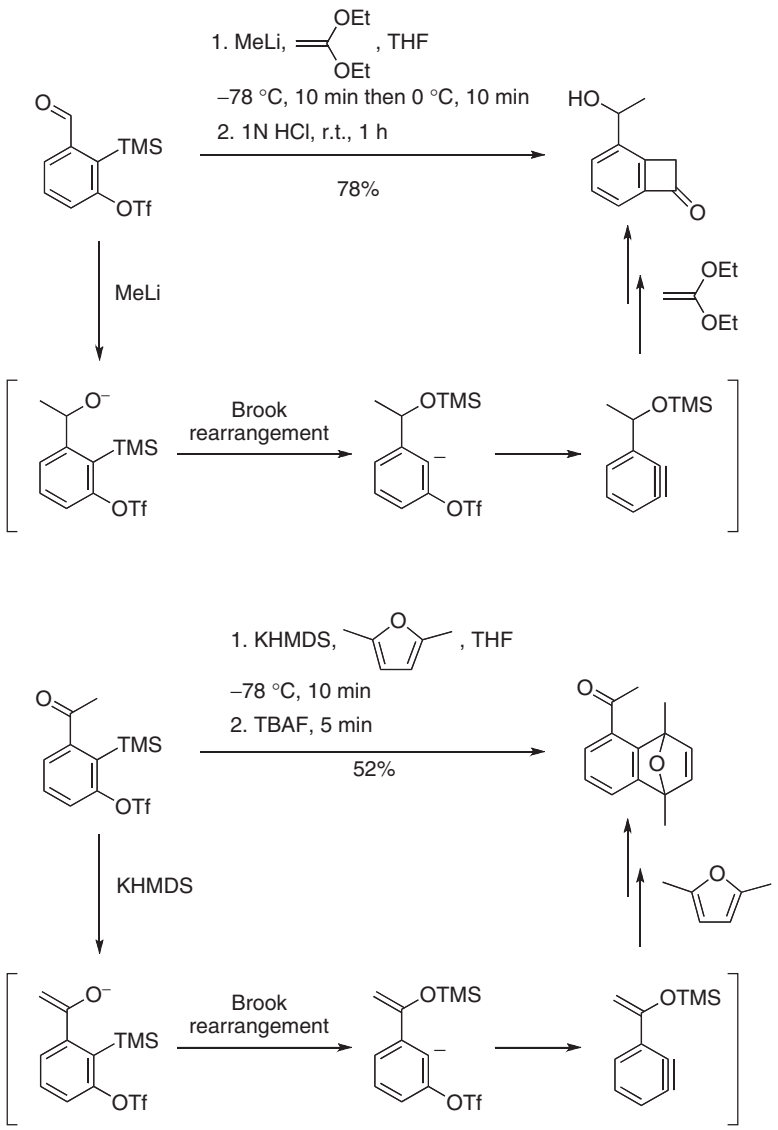


Scheme 8

Diversification of the aryne precursors has been achieved by a number of procedures: corannulyne **5**,[66] indolyne **7**,[67–69] bisaryne **8**,[70] **9**,[71] trisaryne **10**,[72] etc. can be smoothly produced according to the fluoride-mediated aryl–silicon bond cleavage (equation 4). Furthermore, uniting the aryne precursors having a carbonyl moiety at the *ortho*-position with anion relay chemistry has recently been developed, where the [1,4]-Brook rearrangement triggers the aryne generation (Scheme 9).[73]

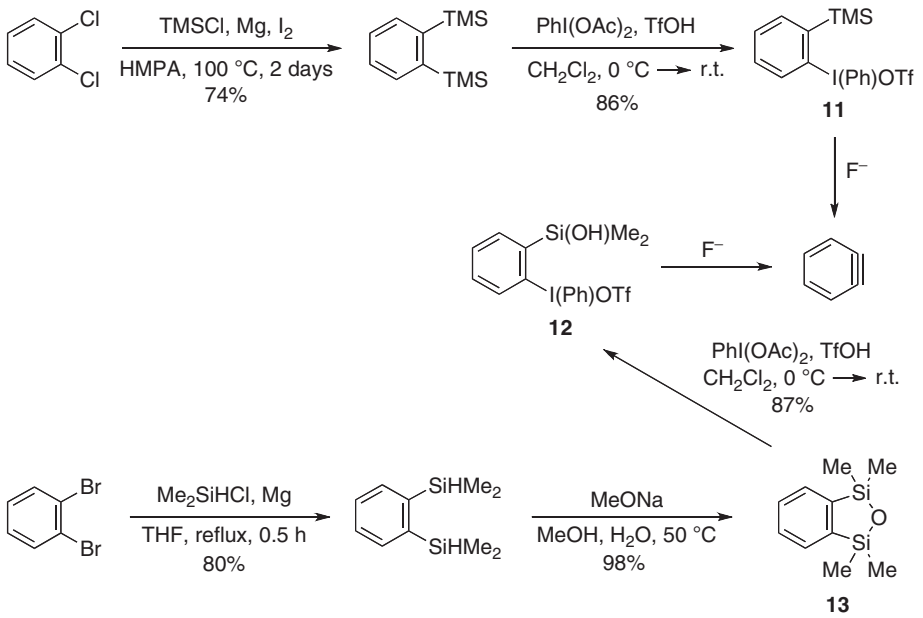

5
7
8
TMS
OTf
F⁻
9
10

(4)


1. MeLi,
OEt
OEt
, THF
–78 °C, 10 min then 0 °C, 10 min
2. 1N HCl, r.t., 1 h
78%
HO
O
TMS
OTf
MeLi
OEt
OEt
O⁻
Brook
rearrangement
OTMS
1. KHMDS,
O
, THF
–78 °C, 10 min
2. TBAF, 5 min
52%
KHMDS

Scheme 9

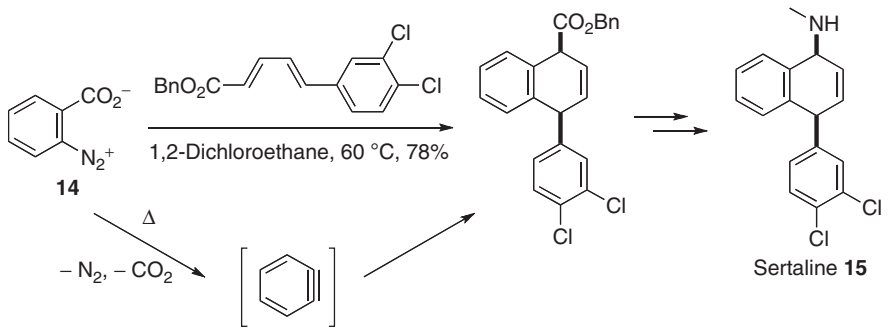
In addition to OTf, a hypervalent iodonium moiety, (IPh)OTf, acts as an excellent leaving group in the fluoride-induced aryne formation. The hypervalent iodine aryne precursors (**11** and **12**) have originally been prepared from 1,2-bis(trimethylsilyl)-arenes,[74–81] whose synthesis requires severe conditions; however, an improved approach using benzoxadisilole **13** is also available (Scheme 10).[82–86]



Scheme 10

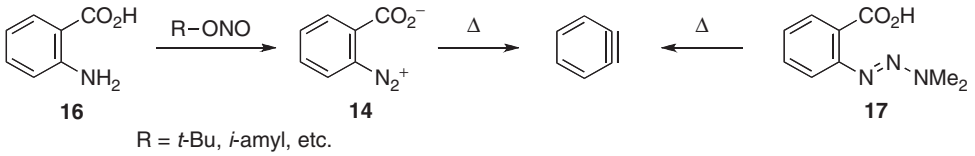
4.09.2.3 Thermolysis

Because of high availability of the starting anthranilic acid derivatives, thermolysis of arenediazonium 2-carboxylates **14** would be a convenient way for the generation of arynes,[87–89] and reliability of this method allows its utilization to total synthesis of an antidepressant, sertraline **15** (Scheme 11).[90]

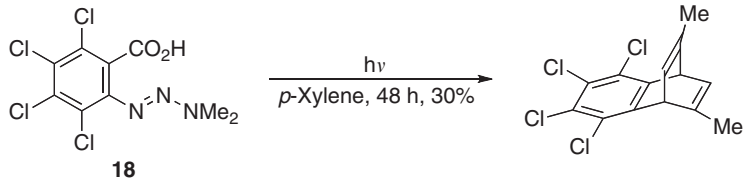


Scheme 11

Although the explosive nature of **14** is the major disadvantage of this method, *in situ* generation of **14** by diazotization of anthranilic acids **16** with an alkyl nitrite[91] and the use of stable aryne precursors, 1-(2′-carboxyaryl)-3,3-dimethyltriazenes **17**,[92] have been recognized as safer alternatives (Scheme 12). Interestingly, 1-(2′-carboxytetrachlorophenyl)-3,3-dimethyltriazene **18** undergoes photolysis as well to give the aryne, whereas 1-(2′-carboxyphenyl)-3,3-dimethyltriazene is recovered unchanged under the same conditions (equation 5).

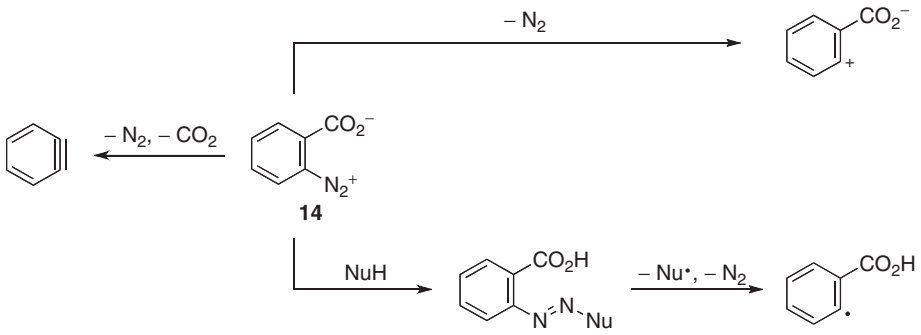


Scheme 12



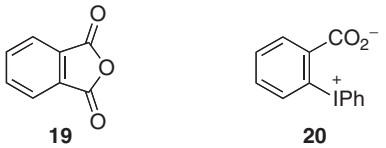
(5)

Since various factors including solvents, reagents, and substituents on the aromatic rings of **14** affect the course of the thermolysis, and the decomposition to arynes sometimes competes with formation of 2-carboxyaryl cation and/or 2-carboxyaryl radical intermediates,[93] products arising from these intermediates are occasionally generated depending on reaction conditions in the nucleophilic coupling using **14** (Scheme 13).[94]



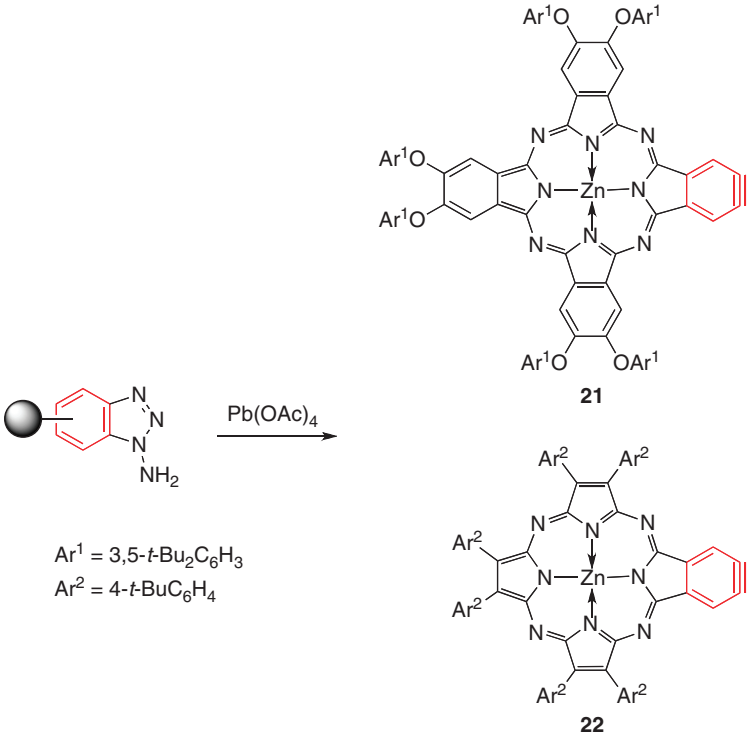
Scheme 13

Phthalic anhydride **19**[95] and 1-(phenyliodonio)arene-2-carboxylate **20**[96] are also thermally decomposed into arynes; however, the relatively harsh reaction conditions result in scarce employment in the nucleophilic coupling.

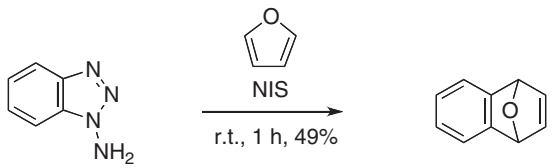


4.09.2.4 Oxidation

Arynes can be generated by oxidation of 1-aminobenzotriazoles with $Pb(OAc)_4$, and this procedure was applicable to generation of zinc didehydrophthalocyanine **21** and zinc didehydroporphyrazine **22** (equation 6).[97] A modified procedure, which employs *N*-bromosuccinimide (NBS) or *N*-iodosuccinimide (NIS) as an oxidant, has been also developed (equation 7).[98] Various benzo-annulated oxygen heterocycles have been synthesized based on this protocol by use of 1-aminobenzotriazoles bearing a hydroxy group in a side chain via intramolecular aryne cyclization (see Section 4.09.3.2.6).



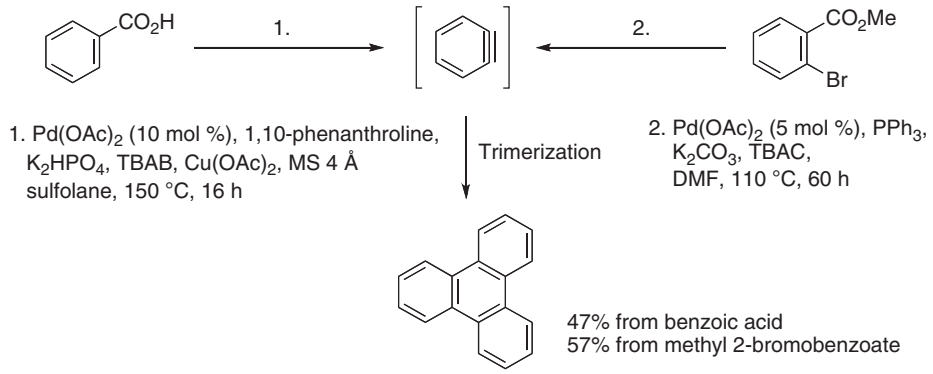
(6)



(7)

4.09.2.5 Transition Metal-Catalyzed Decarboxylation

Benzoic acids[99] and methyl 2-bromobenzoates[100] can also serve as precursors of arynes under palladium catalysis via a decarboxylation reaction. Although these methods opened up a new vista of the catalytic generation of arynes from readily available substrates, their utilization for nucleophilic coupling should be difficult because the resulting arynes undergo the palladium-catalyzed self-trimerization succeedingly (Scheme 14).



Scheme 14

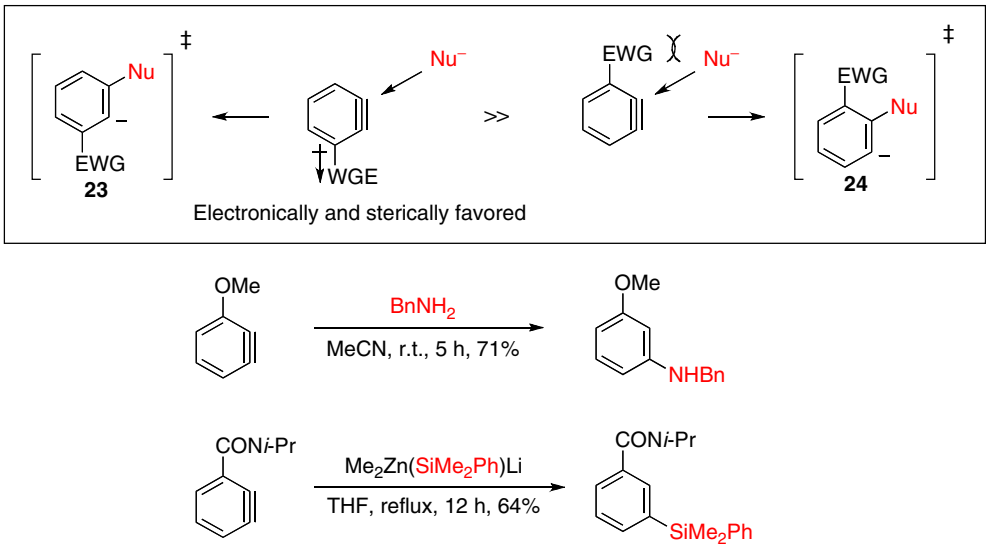
4.09.3 Addition of Nucleophiles to Arynes

4.09.3.1 Regioselectivity in Nucleophilic Addition to Unsymmetrical Arynes

Since both ends of a carbon–carbon triple bond of arynes accept nucleophilic addition, regioselectivity would be a key issue in the nucleophilic coupling with unsymmetrical arynes. Steric and inductive electronic effects of substituents on unsymmetrical arynes govern directions of incoming nucleophiles, whereas their mesomeric (resonance) effect on the regioselectivity is almost negligible because the reacting π-bond is orthogonal to the aromatic π-system. The regioselectivity of the incoming nucleophiles controlled by the inductive effect are predictable by considering polarization of the carbon–carbon triple bond or stabilization/destabilization of a developing aryl anion in transition state, both of which give the similar results. As the regioselectivity is also affected by many factors including nucleophilicity of the nucleophiles, reversibility of the nucleophilic addition step, etc., following discussions focusing on the substituent-dependent regioselectivity just illustrate a general tendency.

4.09.3.1.1 3-Substituted arynes

Arynes bearing such an inductively electron-withdrawing group (EWG) as alkoxy, carbonyl, or halogen generally accept nucleophilic attack at their *meta*-position in high regioselectivity because stabilization of the transition state is more pronounced in **23** than **24**. In addition to this electronic effect, disfavored steric repulsion between the substituent in the arynes and the incoming nucleophiles also orients the nucleophilic attack toward the *meta*-position (Scheme 15).[35,101] The steric effect would mainly control the regioselectivity in the reaction of 3-phenylbenzyne[102] or 1,2-naphthalyne,[103] where *peri* hydrogen shields the addition to the α-position in the latter case (Scheme 16).



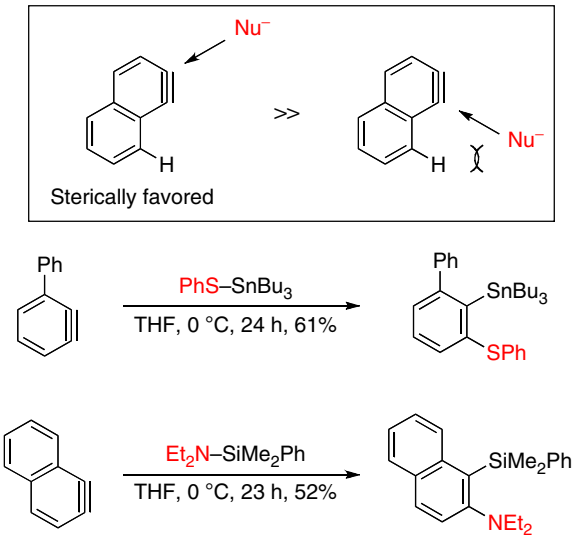
Scheme 15

The repulsive steric effect competes with electron-donating effect of an alkyl group, which prefers generation of the aryl anion at the *meta*-position in the transition state, leading to no consistency in the regioselectivity with 3-alkylarynes depending on the nature of the reagents (Scheme 17).[102,103]

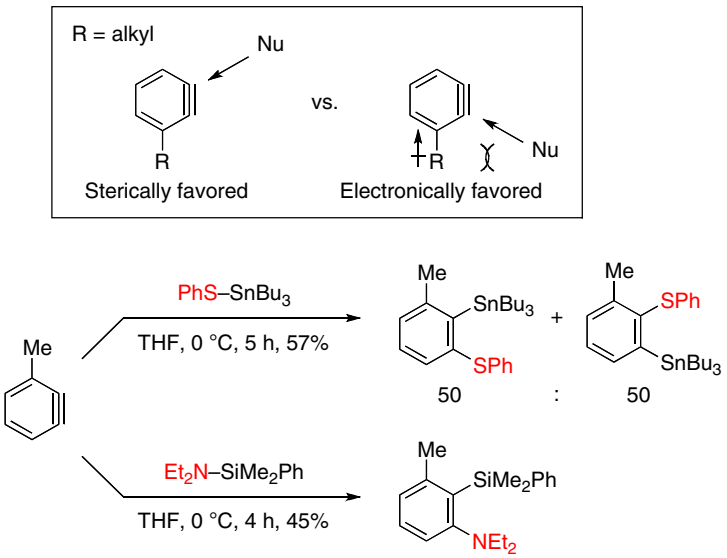
However, high *ortho*-selectivity toward the nucleophilic addition has been achieved with 3-(trimethylsilyl)arynes, showing that the electronic effect overrides the steric disadvantage, which results from increased polarization of the triple bond by the formation of silicate complex **25** with a fluoride used as an aryne generator (Scheme 18).[104] Regardless of the electron-donating character of the alkyl group, *meta*-selective addition is observed with cyclobutane-fused benzyne, being ascribable to an enhanced s character of an orbital bound to the α carbon, whereas cyclopentane-fused benzyne gives an equal amount of regioisomers (Scheme 19).[105]

4.09.3.1.2 4-Substituted arynes

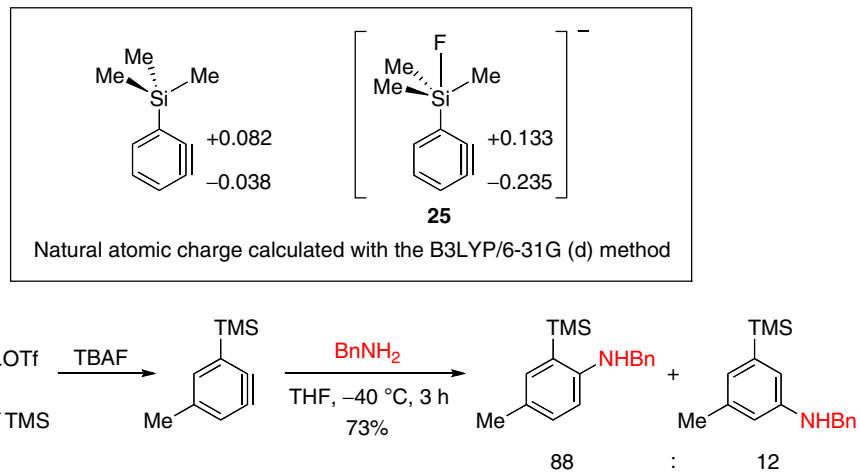
A substituent at a 4-position of arynes exerts steric influence scarcely, and the regioselectivity is totally controlled by an electronic effect. Similar to the cases with the 3-substituted arynes, a developing negative charge at a closer position to an EWG is stabilized to some extent in the transition state for the nucleophilic attack, which results in the preferential addition of nucleophiles to the *para*-position, although the impact on the regioselectivity is less pronounced than that of the 3-substituent. As shown in Scheme 20, the magnitude of *para*:*meta* product distribution in the reaction of 4-haloarynes parallels the electronegativity (F, 72:28; Cl, 64:36; Br, 59:41; I, 52:48).[30] However, a substituent of a weak inductive effect like methoxy and methyl moiety



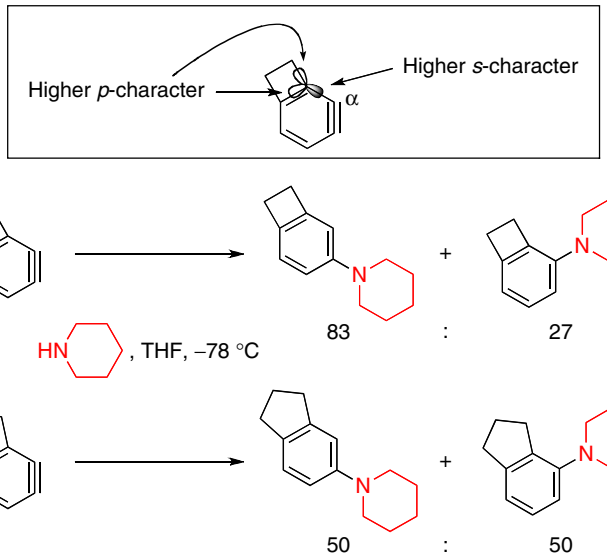
Scheme 16



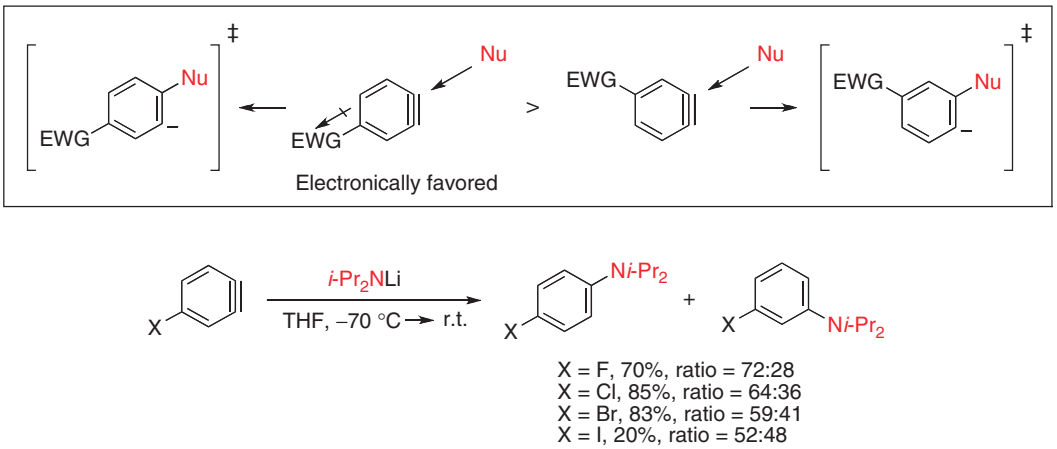
Scheme 17



Scheme 18

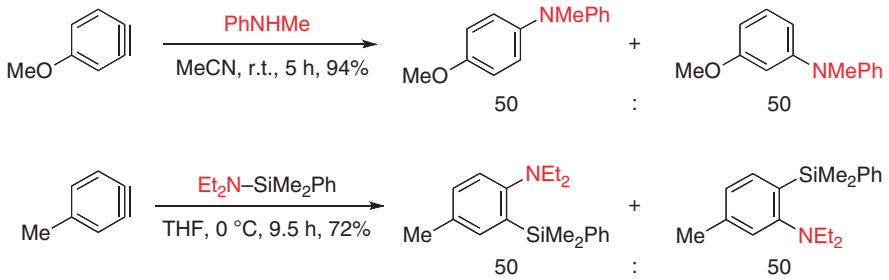


Scheme 19



Scheme 20

seldom induce an electronic difference in the triple bond, and thus, the nucleophilic attack occurs on both ends equally in many cases (Scheme 21).[101,103]

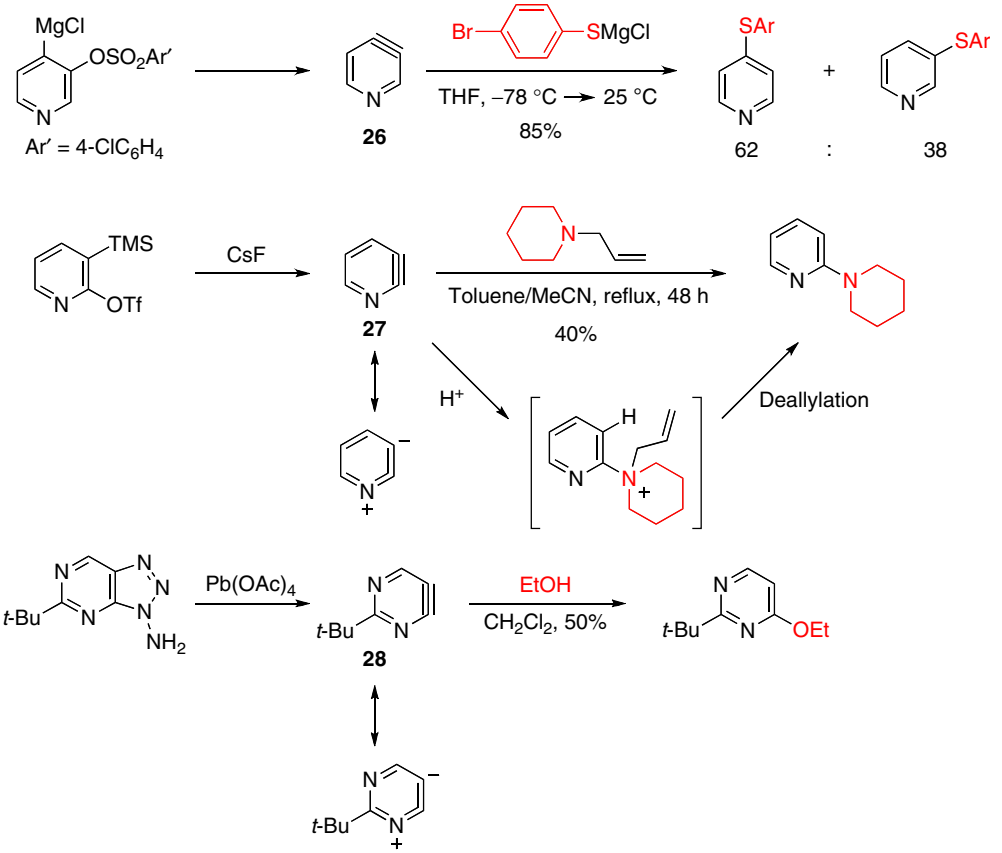


Scheme 21

4.09.3.1.3 Heteroarynes

The regioselectivity trend in the nucleophilic addition to 3,4-pyridyne **26** is similar to that observed with 4-haloarynes, which results in the preferential formation of *para*-substituted pyridines.[54] Because a cumulenic resonance structure of 2,3-pyridyne **27**

exerts significant effect on the regioselectivity, the nucleophilic coupling at the *ortho*-position takes place in a highly regioselective manner,[106] and the regioselectivity with 4,5-pyrimidyne **28** is also governed by the cumulenic structure (Scheme 22).[107,108]



Scheme 22

The regiochemical outcome of the reaction using various indolynes has been explained by difference in internal angles of the indolynes obtained from quantum chemical calculations, where flatter or more distorted end of the carbon–carbon triple bond of indolynes is apt to be coupled with nucleophile;[68,69] however, arguments based on the above electronic/steric effect lead to similar predictions (Scheme 23).

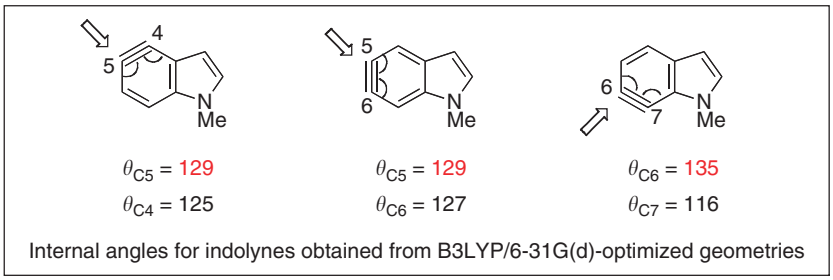
4.09.3.2 Use of Nucleophilic Coupling with Arynes in Synthesis

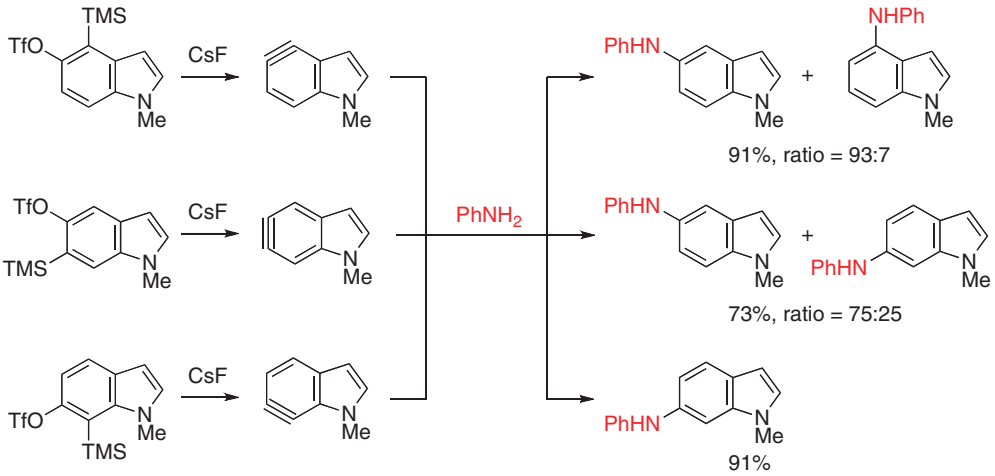
Because of the highly electrophilic character of arynes, a variety of anionic and even neutral nucleophiles readily react with arynes to give substituted arenes and benzo-annulated systems of structural complexity and diversity. All of the reactions proceed through formation of aryl anions (from anionic nucleophiles) or zwitterions (from neutral nucleophiles) as common intermediates by the nucleophilic attack of nucleophiles to arynes and can be classified into six categories depending on reaction modes (Scheme 24):

1. Simple arylation of nucleophiles via protonation of the aryl anionic moieties.
2. Insertion into a σ-bond between a nucleophilic and an electrophilic moiety (*Nu–El*), which proceeds through intramolecular nucleophilic substitution.
3. Annulation by use of nucleophiles bearing an electrophilic moiety at a suitable position.
4. Multicomponent coupling through capturing the aryl anionic moieties with a third component (electrophile).
5. [2 + 2] Cycloaddition using a nucleophilic–electrophilic double bond (*Nu*=*El*).
6. Intramolecular cyclization with aryne-tethered nucleophiles.

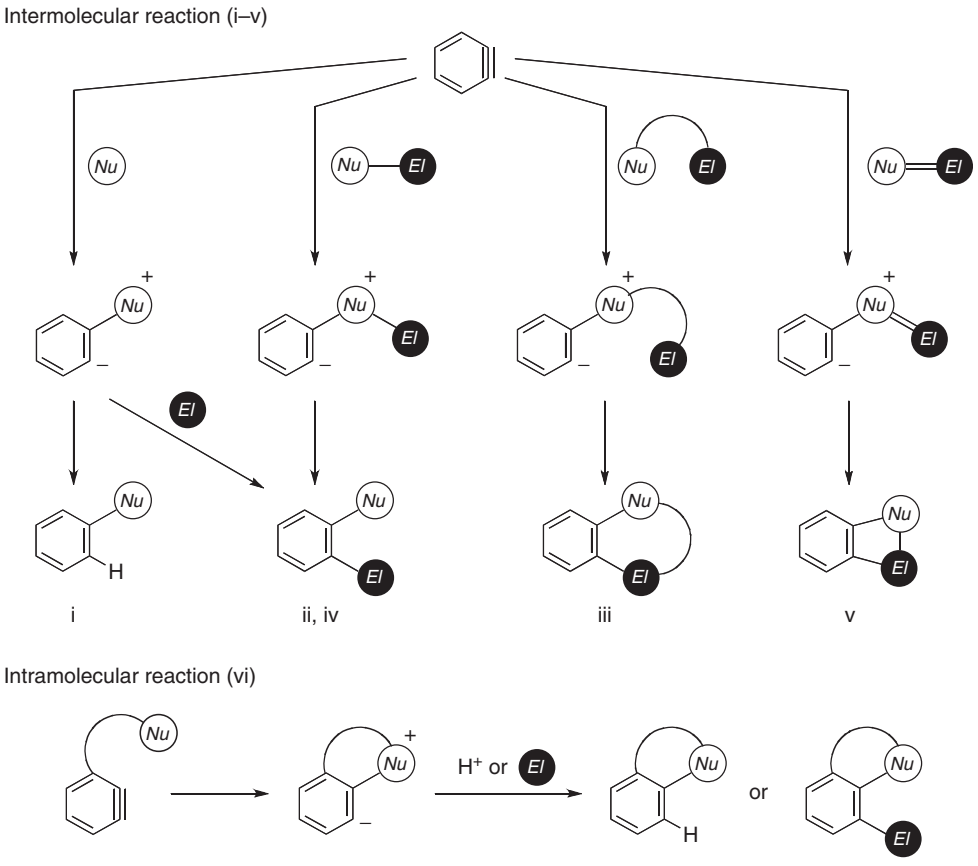
4.09.3.2.1 Simple arylation

Much attention has been focused on the *N*-arylation of amines with aryl halides (or triflates) under the aryne generation conditions (see Section 4.09.2.1.1),[29,30,34,109,110] which complements the Ullmann-type amination and the Buchwald–Hartwig





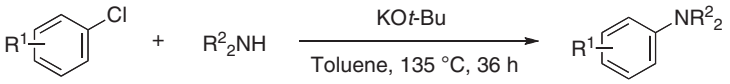
Scheme 23

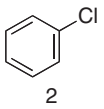
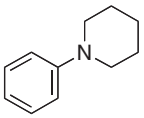
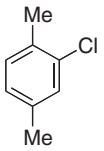
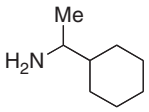
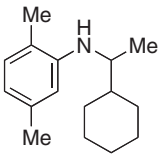
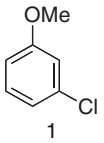
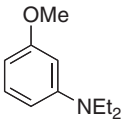
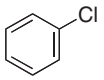
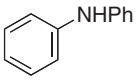
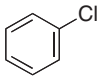
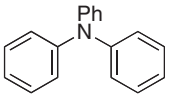


Scheme 24

amination. In view of the fact that the *N*-arylation of amines with arynes can be conducted in the absence of a transition metal catalyst like copper and palladium, its synthetic utility is quite high if regioselectivity is perfectly controlled. A variety of aliphatic and aromatic amines can undergo the *N*-arylation with aryl chlorides using KO*t*-Bu as a base to give the respective products in high yield, and mono- or diphenylation of aniline is controllable by simply changing molar amounts of chlorobenzene (Table 1).[111] The reaction can also be applied to 1,3-dichlorobenzene and 1,3,5-trichlorobenzene to provide 1,3-diaminobenzene and 1,3,5-triaminobenzene regioselectively (Scheme 25), being ascribable to the selective formation of 3-chloro- and 3-aminobenzyne as well as the regioselective addition of amines to them (see Section 4.09.3.1.1).

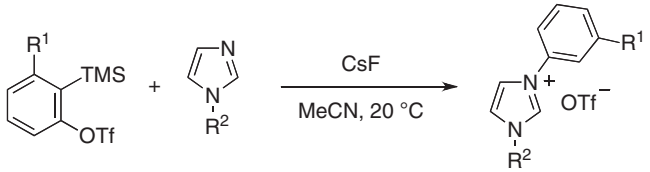
Table 1 *N*-arylation of amines with KO*t*-Bu



Aryl chloride (eq)	*Amine (eq)*	*Product*	*Yield (%)*
 2	1		85
 2	 1		59
 1	Et_2NH 2		93
 2	$PhNH_2$ 1		81
 3	$PhNH_2$ 1		78

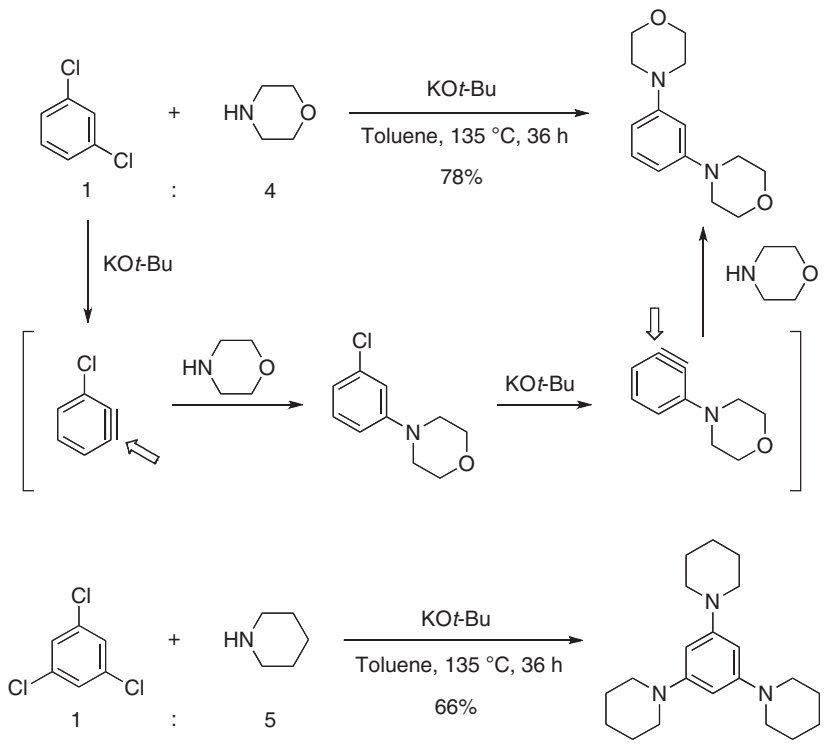
Potassium hydroxide in dimethyl sulfoxide (DMSO) serves as an efficient base for the *N*-arylation process: not only simple amines but also *N*-heterocycles such as pyrazol, imidazole, and indole smoothly participate in the reaction (Table 2).[112] A similar *N*-arylation with 3,4-pyridynes that produces regioisomeric mixtures in most cases,[113–115] and the utilization for synthesis of oxaza adamantyl cannabinoids representing a new class of ligands for the CB1 and CB2 receptors have been reported (Scheme 26).[116]

The use of 2-(trimethylsilyl)aryl triflates as an aryne precursor in the *N*-arylation[104] improves the functional group compatibility to a great extent: base-sensitive substituents such as CN, CO_2Et, Ac, NHAc, I, etc. remain intact throughout the reaction, and allyl and propargyl amines are smoothly arylated without undergoing ene reaction with arynes (Table 3).[101,117] Sulfonamides[101,117] and *N*-alkylimidazoles also take part in the *N*-arylation, in the latter of which *N*-alkyl-*N*′-arylimidazolium salts are formed (equation 8).[118]



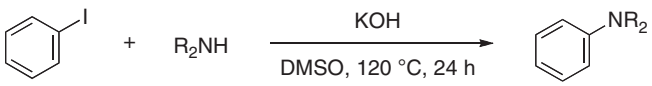
(8)

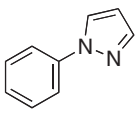
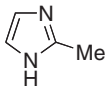
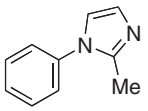
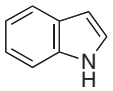
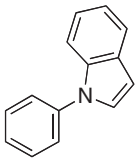
R^1 = H, R^2 = CH_2OMe, 14 h, 59%
R^1 = H, R^2 = *t*-Bu, 19 h, 53%
R^1 = OMe, R^2 = Me, 17 h, 56%



Scheme 25

Table 2 *N*-arylation of amines with KOH/DMSO

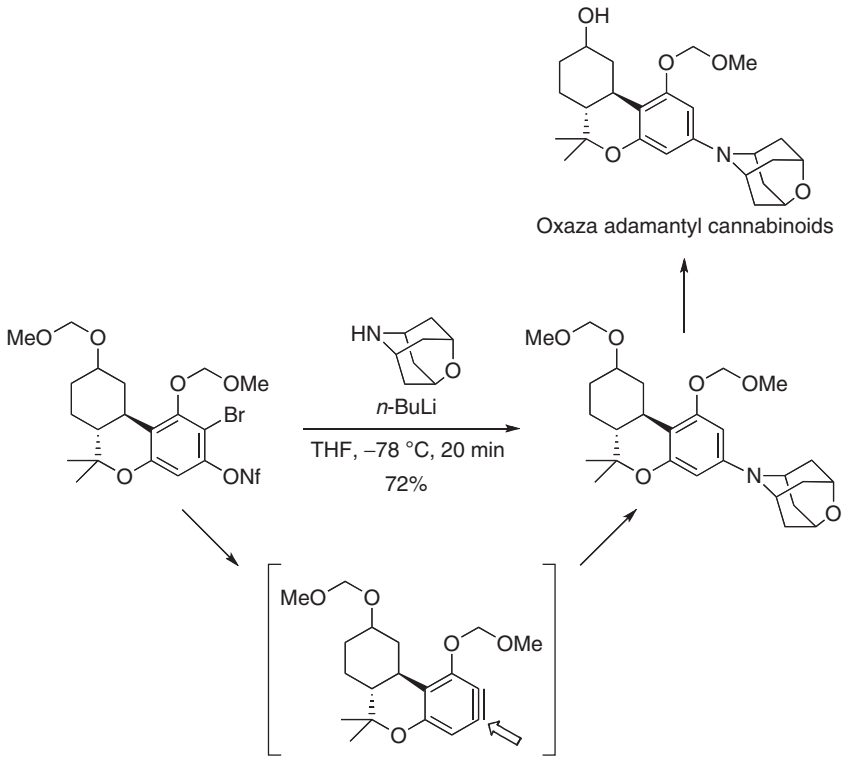


Amine	*Product*	*Yield (%)*
		92
		96[a]
		80

[a]48 h.

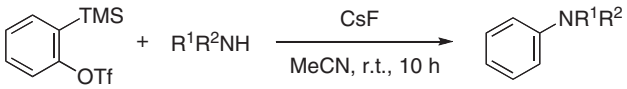
Combining the procedure with the Pd-catalyzed intramolecular cyclization[119,120] or the Fischer cyclization[121] enables carbazoles or indoles to be synthesized in two steps from 2-iodoanilines or *N*-tosylhydrazones (Scheme 27). In addition, the high functional group compatibility of the *N*-arylation under neutral conditions enables total synthesis of indolactam V by use of indolyne (Scheme 28).[122]

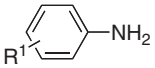
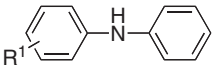
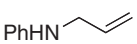
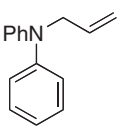
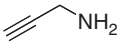
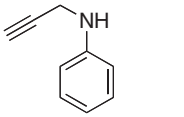
Highly chemoselective *O*- and *S*-arylation take place with 2-(trimethylsilyl)aryl triflates, and thus phenols, carboxylic acids, and thiophenols are readily converted into the arylated products in high yield (Scheme 29).[101,123,124] Two-step synthesis of dibenzofurans from 2-iodophenols according to the above method,[119,120] and quaternization of phosphines and arsines with



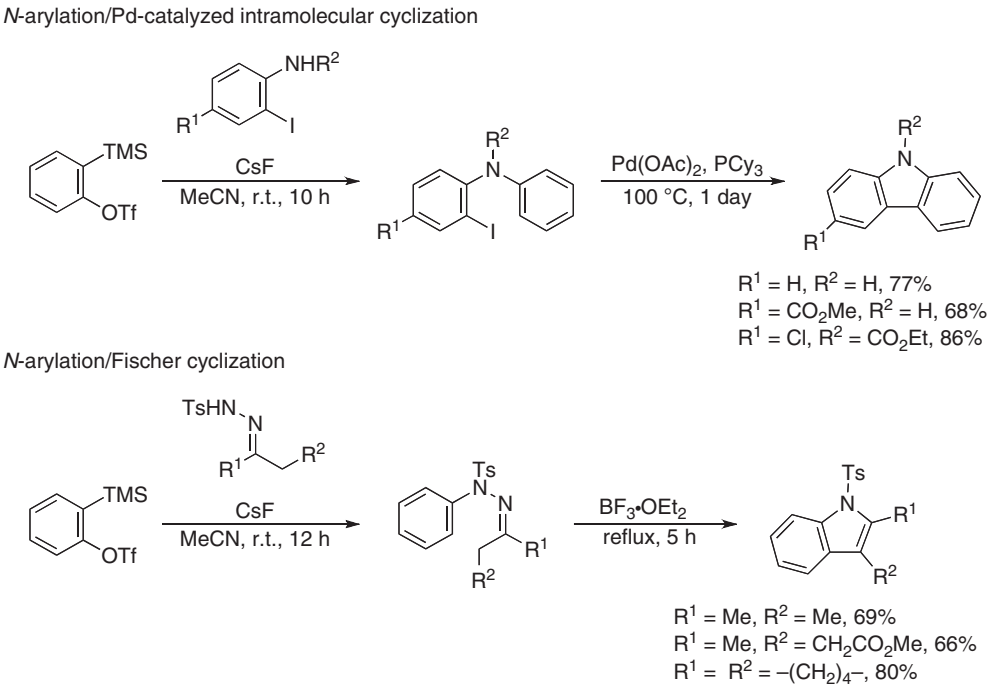
Scheme 26

Table 3 *N*-arylation of amines under neutral conditions

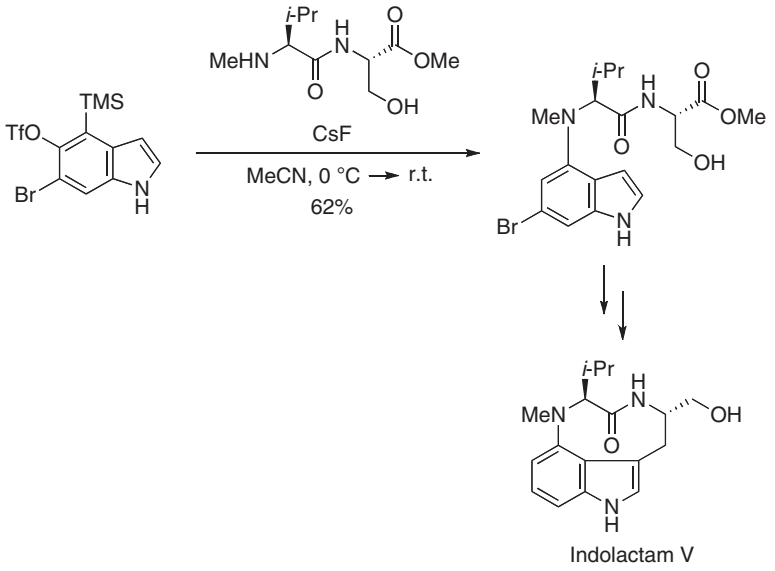


Amine	*Product*	*Yield (%)*
		
	R^1 = 4-CN	90
	4-CO_2Et	94
	4-Ac	94
	3-NHAc	95
	2-I	91
		97[a]
		62[a]

[a] 5 h.



Scheme 27

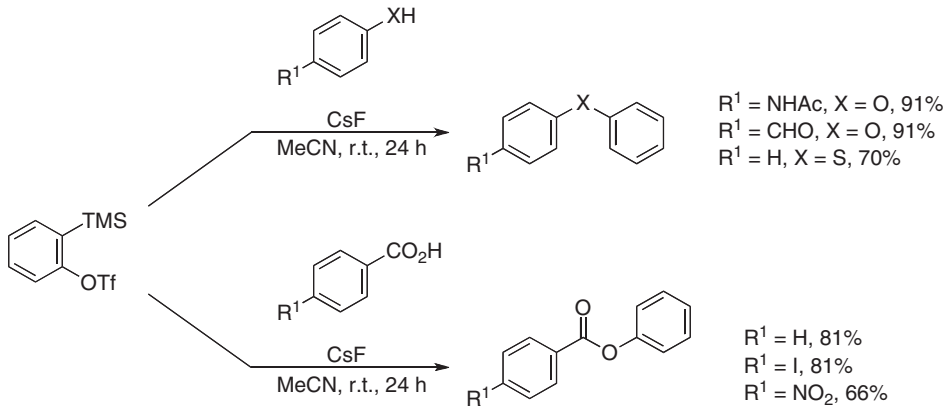


Scheme 28

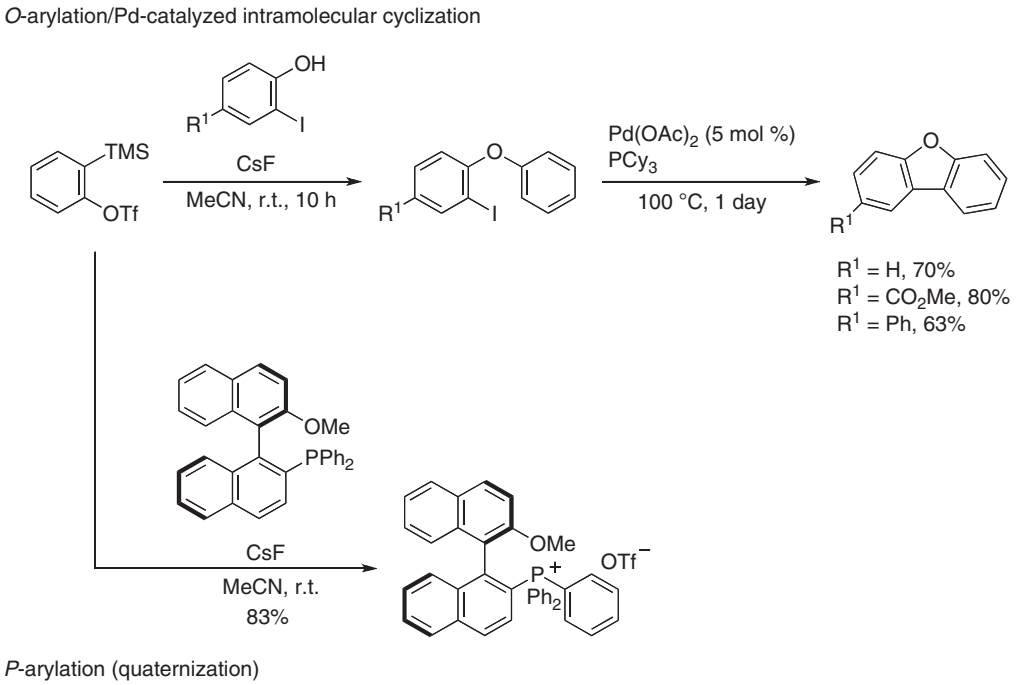
arynes have also been achieved (Scheme 30).[125] The *O*- and *S*-arylation with aryl halides in the presence of KOH in DMSO proceed smoothly.[112,126]

A transition metal-free method for arylation of a C(sp^2)–H bond (heteroarenes)[127] and C(sp)–H bond (alkynes)[128] with aryl chlorides has been developed under the aryne generation conditions (Table 4). In particular, the *C*-arylation with symmetrical arynes or arynes having an electron-withdrawing substituent at the 3-position has high synthetic significance, since a single arylation product is definitely formed in these cases.[129] Similarly, the reaction with 1,3-dichlorobenzene or 1,3-dichloro-2-iodobenzene provides direct routes to *meta*-terphenyls through dual generation of arynes (Scheme 31).[130–133]

A C(sp^3)–H bond of relatively high acidity in nitriles[134–137] and α,β-unsaturated acids (or amides)[138,139] undergoes the *C*-arylation, resulting in the preferential formation of γ-arylated products in the latter case. Besides, Schöllkopf's bis-lactim ether **29** is convertible into *syn*-arylated products in excellent stereoselectivity,[140] which can be utilized for asymmetric synthesis of arylglycines (Scheme 32).

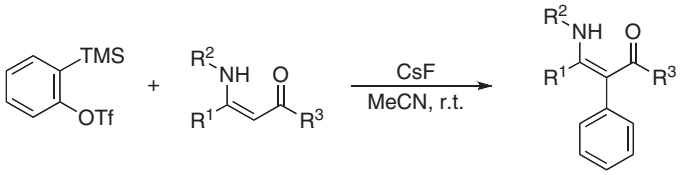


Scheme 29



Scheme 30

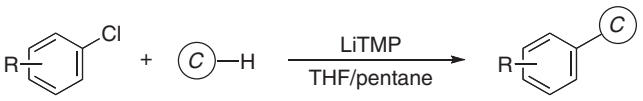
The *C*-arylation of isocyanides with anthranilic acid-derived arynes (see Section 4.09.2.3) provides benzamides via the reaction of intermediary zwitterions **30** with H_2O (Scheme 33),[141] and furthermore various aldehydes undergo the *C*-arylation at their carbonyl carbons in the presence of an *N*-heterocyclic carbene (NHC) catalyst,[142] where the *in situ*-generated Breslow intermediate (**31**) serves as the nucleophile toward arynes (Scheme 34). An efficient method for the *C*-arylation of *β*-enamino esters and ketones has also been developed,[143] where a free amino and a furan moiety are well tolerated, that is, the *N*-arylation and the Diels–Alder reaction with arynes do not occur at all (equation 9).

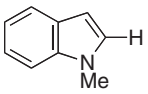
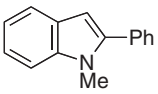
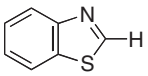
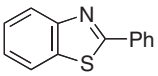
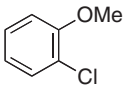
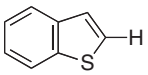
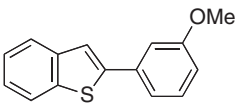
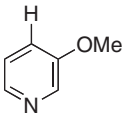
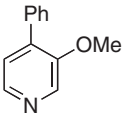
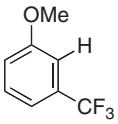
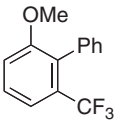
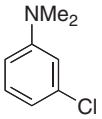
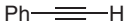
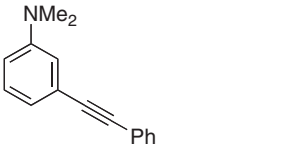
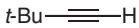
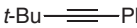
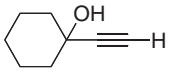
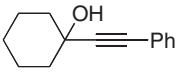


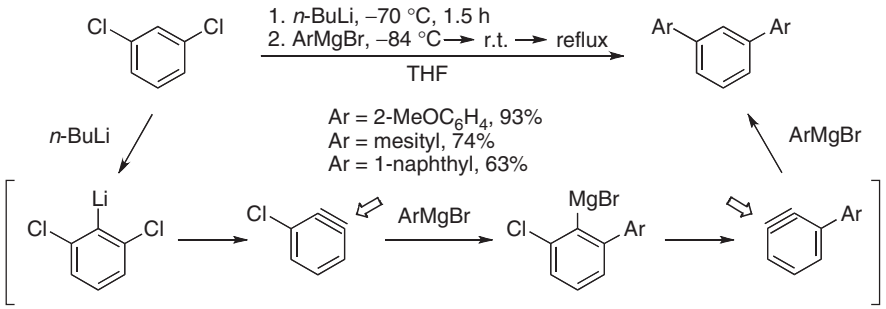
(9)

R^1 = 3-Furyl, R^2 = H, R^3 = OEt, 71%
R^1 = CO_2Me, R^2 = *i*-Pr, R^3 = OMe, 56%
R^1 = Me, R^2 = $(CH_2)_2OH$, R^3 = Me, 90%

Table 4 C-arylation of C(sp^2)–H and C(sp)–H



ArCl	C–H	*Product*	*Yield (%)*
PhCl			90
PhCl			72
			78
PhCl			71
PhCl			81
			85
PhCl			93
PhCl			65

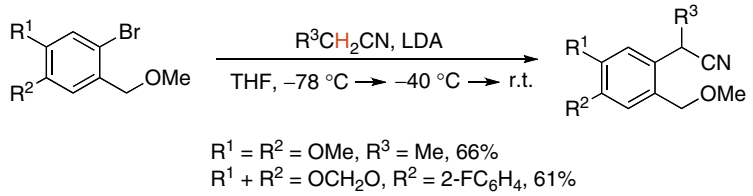


Scheme 31

4.09.3.2.2 Addition of σ-bonds

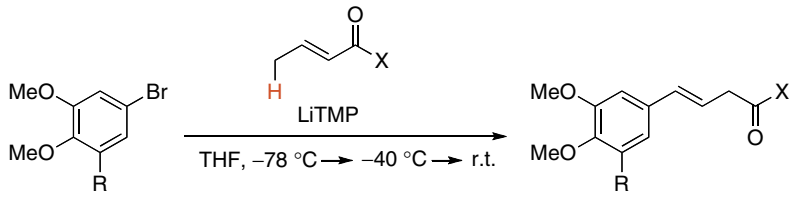
A variety of *ortho*-disubstituted arenes are synthesized straightforwardly depending on the insertion of arynes into nucleophilic–electrophilic σ-bonds (*Nu–El*): arynes can be inserted into a N–C bond of cyclic (five- and six-membered) and acyclic ureas to afford aminocarbamoylated products such as benzodiazepines and benzodiazocines in high yields.[144] As described in **Scheme 35**, a urea nitrogen atom adds to an aryne to give zwitterion **32**, which furnishes the product by intramolecular nucleophilic substitution at the carbonyl carbon atom.

Nitrile



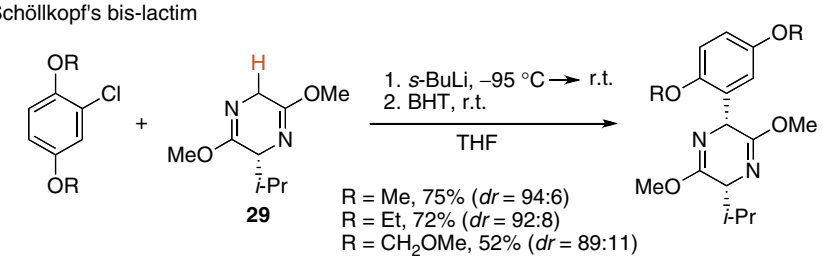
$R^1 = R^2 = OMe$, $R^3 = Me$, 66%
$R^1 + R^2 = OCH_2O$, $R^2 = 2\text{-}FC_6H_4$, 61%

α,β-Unsaturated amide (acid)



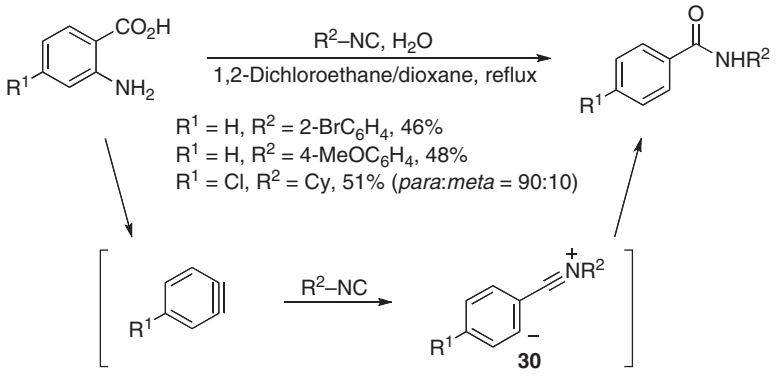
R = H, X = NH(4-$MeOC_6H_4$), 67%
R = OMe, X = OH, 63%

Schöllkopf's bis-lactim



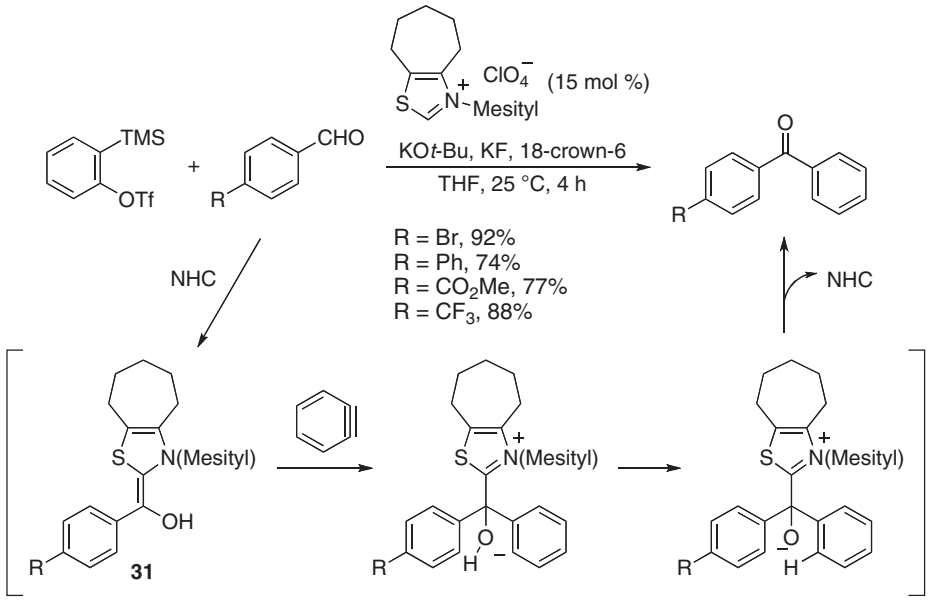
R = Me, 75% (*dr* = 94:6)
R = Et, 72% (*dr* = 92:8)
R = CH_2OMe, 52% (*dr* = 89:11)

Scheme 32

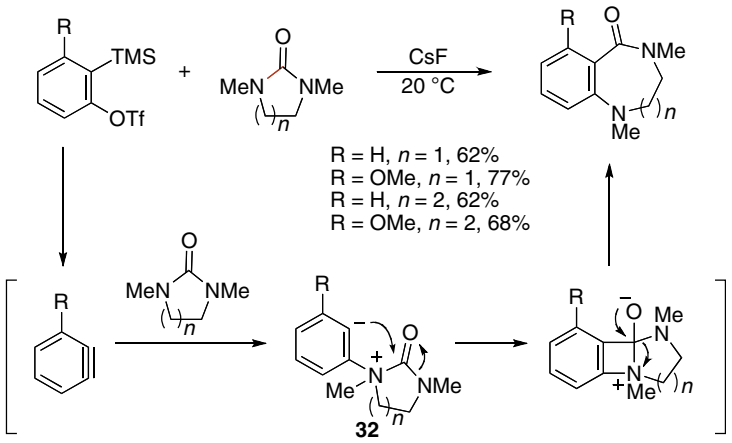


Scheme 33

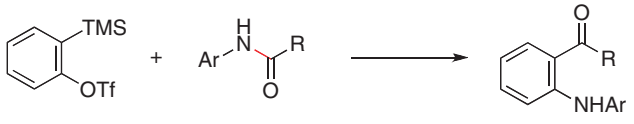
A similar insertion into a N–C bond of trifluoroacetamides, pivalamides, and benzamides takes place smoothly with high functional group compatibility (equation 10),[145,146] and the reaction with benzamides is applicable to two-step synthesis of acridones **33** or acridanes **34** via intramolecular S_NAr reaction or Friedel–Crafts acylation, respectively (Scheme 36). A nitrogen atom of trifluoromethanesulfinamides (N–S bond)[145] and aminosilanes (N–Si bond)[103] also serves as the nucleophilic site for the aryne insertion reaction (Scheme 37), and furthermore a formal insertion into a N–C(allyl) bond of tertiary allylamines proceeds through initial formation of ammonium salt **35** and subsequent charge-accelerated aza-Claizen rearrangement (Scheme 38, path A).[106] In this reaction, 6-*endo* S_N2' reaction of zwitterion **36** is not operative (path B).



Scheme 34



Scheme 35

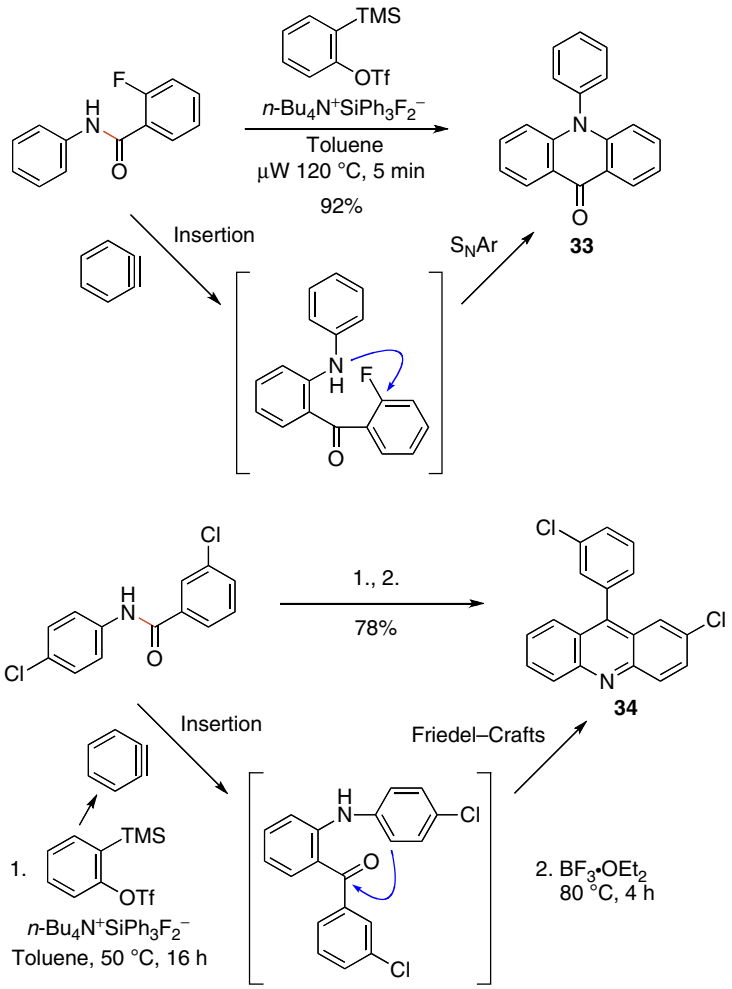


(10)

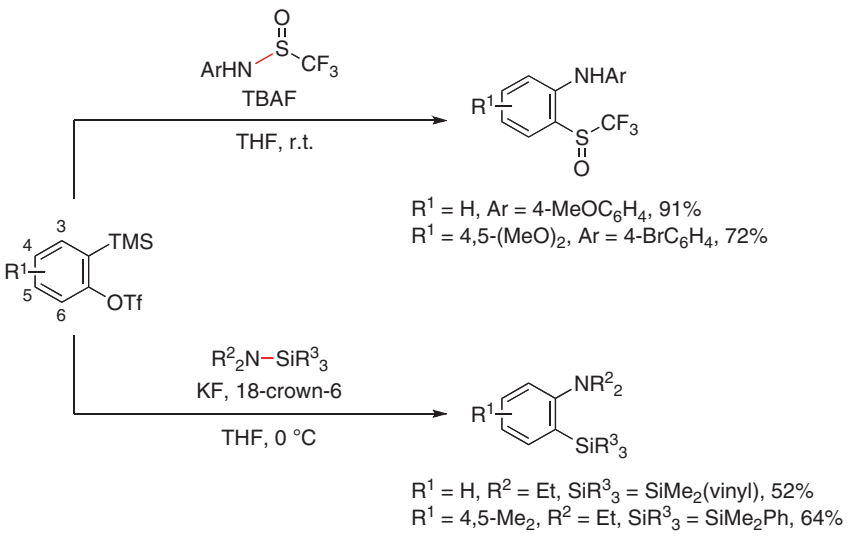
R = CF_3, Ar = Ph, 77% (CsF, MeCN, r.t., 4 h)
R = *t*-Bu, Ar = 4-(EtO_2C)C_6H_4, 71% (*n*-$Bu_4N^+SiPh_3F_2^-$, toluene, 50 °C, 16 h)
R = Ph, Ar = 4-IC_6H_4, 81% (*n*-$Bu_4N^+SiPh_3F_2^-$, toluene, 50 °C, 16 h)

Epoxides[147] and carboxylic acids[148] undergo the insertion of arynes into an O–C bond to provide benzofurans and *ortho*-hydroxyaryl ketones (Scheme 39). It should be noted that the solvents employed definitely alter the course of the reaction of carboxylic acids with arynes (THF: insertion into an O–C bond vs. MeCN: *O*-arylation[101,123] (see Section 4.09.3.2.1)). The intermediary phenolate (**37**) can enjoy further transformation (intramolecular S_NAr reaction or Michael addition) by employing *ortho*-halobenzoic acids, methacrylic acids, or 2-butynoic acids, giving xanthones **38**, 4-chromanones **39**, or flavones **40** (Scheme 40).

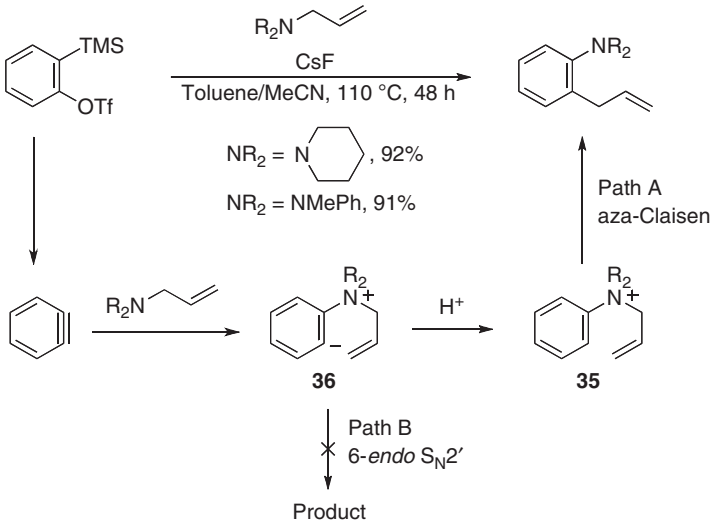
Although arynes can be inserted into an O–C(sp) bond of ethoxyacetylene,[149] the regioselectivity observed in the reaction with 3-methoxybenzyne and density functional theory calculations have verified that the reaction commences with the



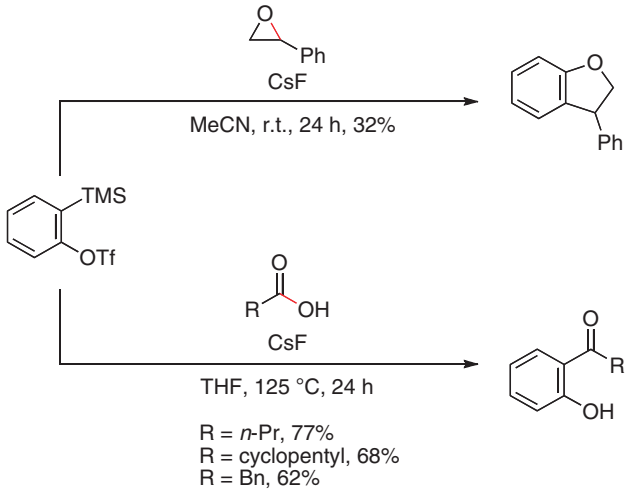
Scheme 36



Scheme 37



Scheme 38

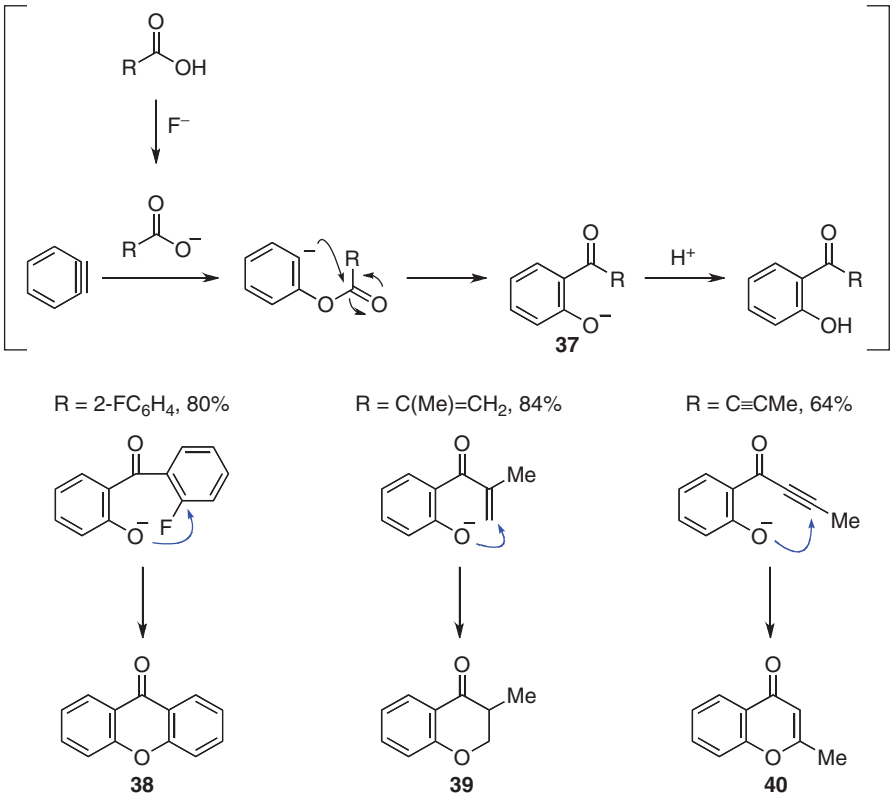


Scheme 39

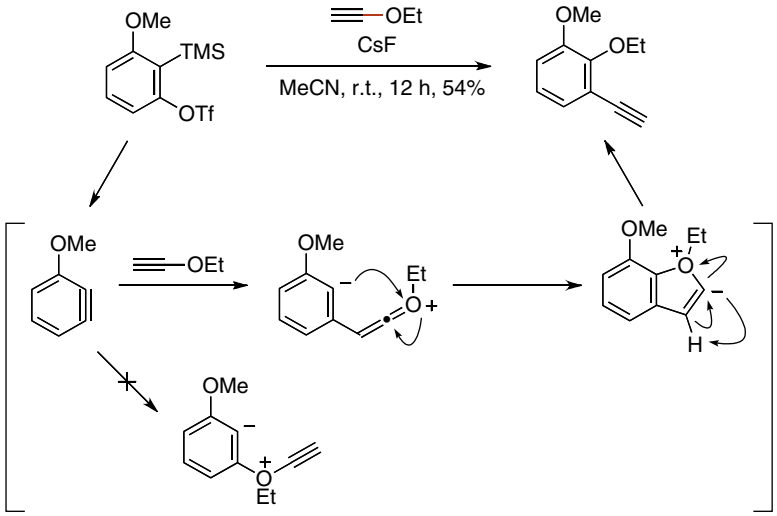
nucleophilic addition of the C–C triple bond (not the oxygen atom), which is totally different from the routine mechanism (Scheme 41). A *Nu–El* σ-bond bearing other chalcogen atoms also participates in the reaction, and thus stannylsulfides (S–Sn bond),[102] thiobismuthanes (S–Bi bond),[150] stannylselenides (Se–Sn bond),[151] and diselenides (Se–Se bond)[152] readily react with arynes to afford the insertion products (Scheme 42).

The prominent electrophilicity of arynes enables even a halogen moiety to serve as a nucleophilic site in the insertion reaction. Thus, the insertion into a Cl–C bond takes place smoothly by the reaction of arynes with various acid chlorides possessing a bromo, cyano, or methoxycarbonyl substituent without injuring these functional groups,[153] which demonstrates the high functional group-compatibility of the reaction. Acid bromides, chloroformates, and carbamoyl chlorides also react with arynes at their halogen–carbonyl bonds exclusively to provide the insertion products, where the respective oxygen–carbonyl and nitrogen–carbonyl bonds remain unchanged in the latter cases (Table 5). Similarly, electron-deficient *N*-heteroaromatics, chlorotriazines undergo the insertion of arynes at the Cl–C(sp^2) bond,[154] however, the reaction is triggered not by formation of zwitterion **41** but by nucleophilic attack of an *in situ*-generated chloride ion to arynes (Scheme 43).

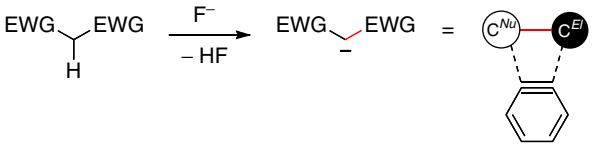
Because deprotonation of an active methylene moiety by a fluoride ion of moderate basicity can generate a carbanionic species *in situ*, which can play a similar role to the above nucleophilic heteroatoms, diverse active methylene compounds are appropriate reagents for the insertion reaction of arynes into their active methylene carbon (C^{Nu}, potentially nucleophilic)–electron-withdrawing carbon (C^{El}, electrophilic) bonds (equation 11). The insertion reaction into a C–C bond provides new organic transformations for constructing complex carbon frameworks through two C–C bond-forming processes, and thus, is of high synthetic significance.



Scheme 40

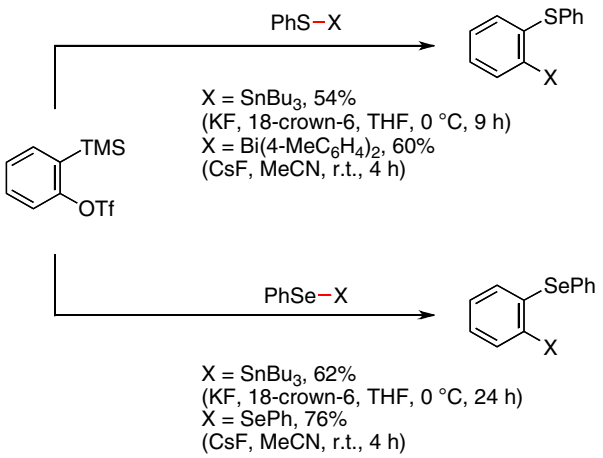


Scheme 41



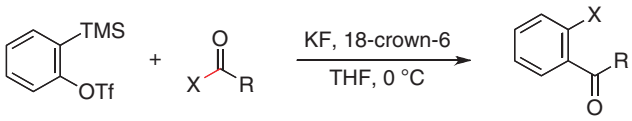
(11)

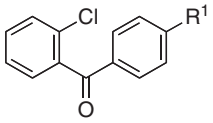
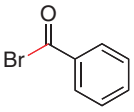
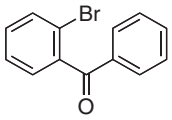
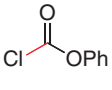
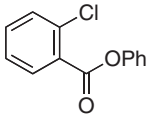
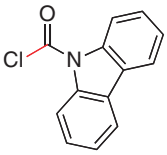
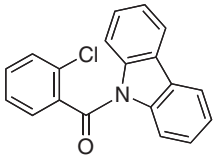
Arynes are smoothly inserted into a C(methylene)–C(ketone carbonyl) bond of β-ketoesters under neutral conditions,[155] and products arising from the insertion into a C(methylene)–C(ester carbonyl) bond are not formed at all. The mild reaction



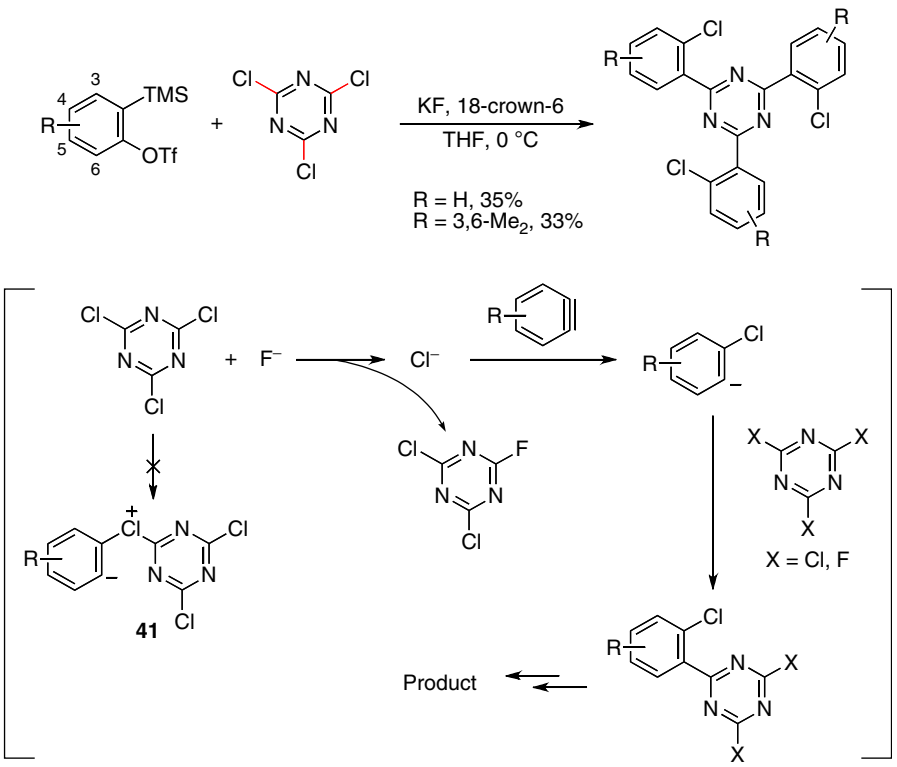
Scheme 42

Table 5 Insertion into C-halogen bond

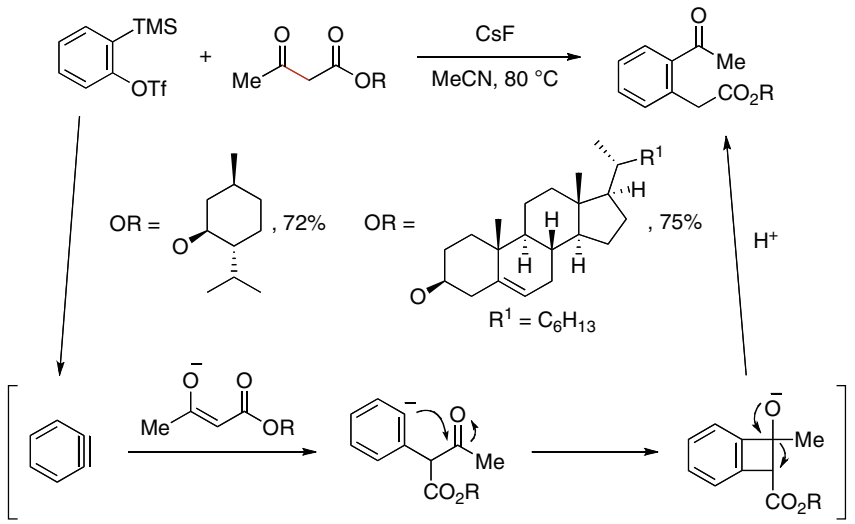


	Product			*Yield (%)*
		R^1 = Br R^1 = CN R^1 = CO_2Me	R^1 = Br R^1 = CN R^1 = CO_2Me	61 54 51
				54
				64
				53

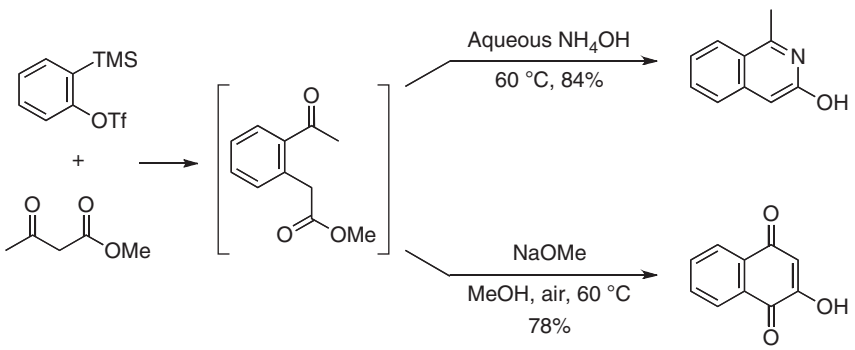
conditions allow the use of complex β-ketoesters: those having menthol or cholesterol moiety provide the insertion products in good yield, and furthermore cyclic β-ketoesters undergo ring expansion to afford medium-sized carbocycles. The reaction proceeds through a formal [2 + 2] cycloaddition between arynes and *in situ*-generated enolates/ring-opening sequence as shown in Scheme 44. The versatility of this method has been demonstrated by total synthesis of (+)-amurensinine (**42**),[156,157] (–)-curvularin (**43**),[158] curvulin (**44**),[158] cytosporone B (**45**),[159] and phomopsin C (**46**),[159] and by synthetic transformation of the insertion products into 3-hydroxyisoquinolines and 2-hydroxy-1,4-naphthoquinones (Scheme 45).[160]



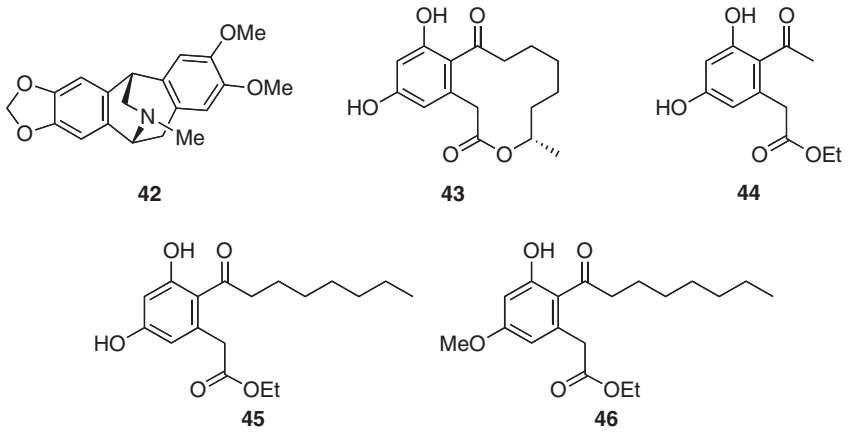
Scheme 43



Scheme 44

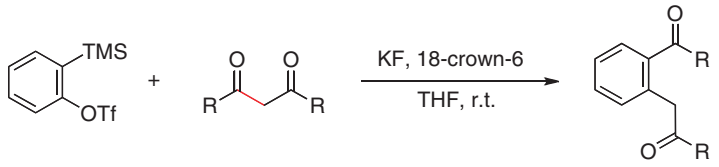


Scheme 45

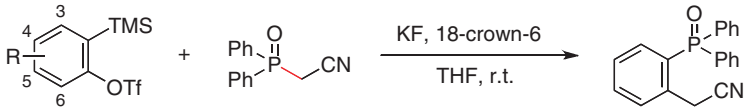


42 **43** **44** **45** **46**

Other β-dicarbonyl compounds including malonates and β-diketones are also subject to the insertion of arynes, and benzo-annulated macrocyclic structures (**47** and **48**) can be fabricated depending on the reaction (equation 12).[161] In addition, the procedure is applicable to α-cyanoketones,[162] β-ketophosphonates,[163] and β-ketosulfones,[164–166] where the C(methylene)–C(carbonyl) bonds are selectively cleaved and added across arynes in all cases (**Scheme 46**). The reaction with β-ketosulfones in the presence of electron-deficient alkenes provides a direct approach to multisubstituted naphthalenes (**Scheme 47**).[164] In contrast, selective insertion into a C(methylene)–P bond takes place by use of cyanomethyldiphenylphosphine oxide as an active methylene compound (equation 13).[167]



(12)



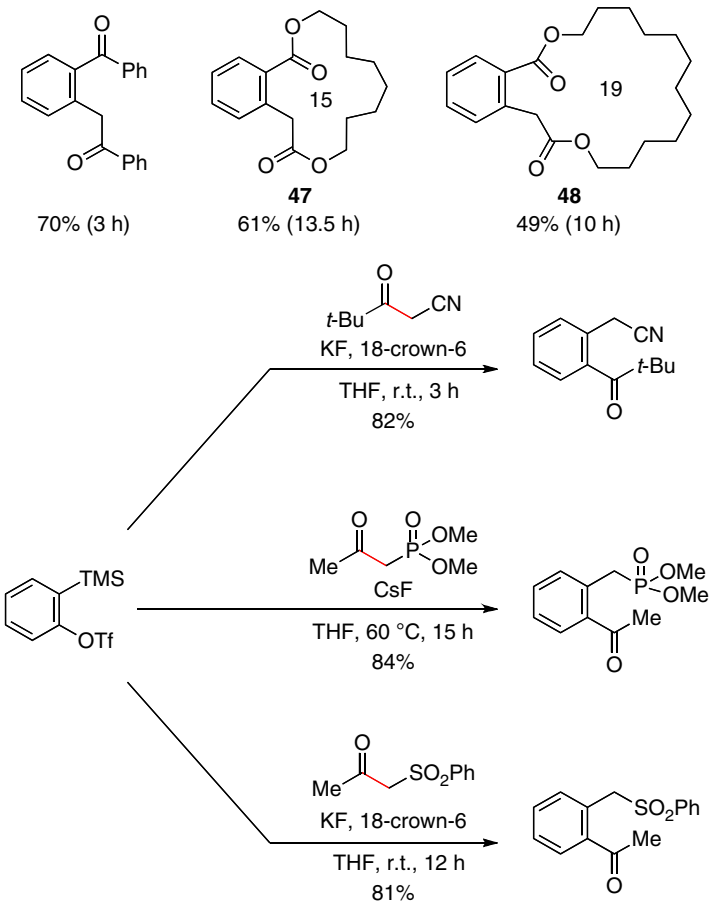
(13)

R = H, 67% (20 h)
R = 4,5-Me_2, 43% (24 h)

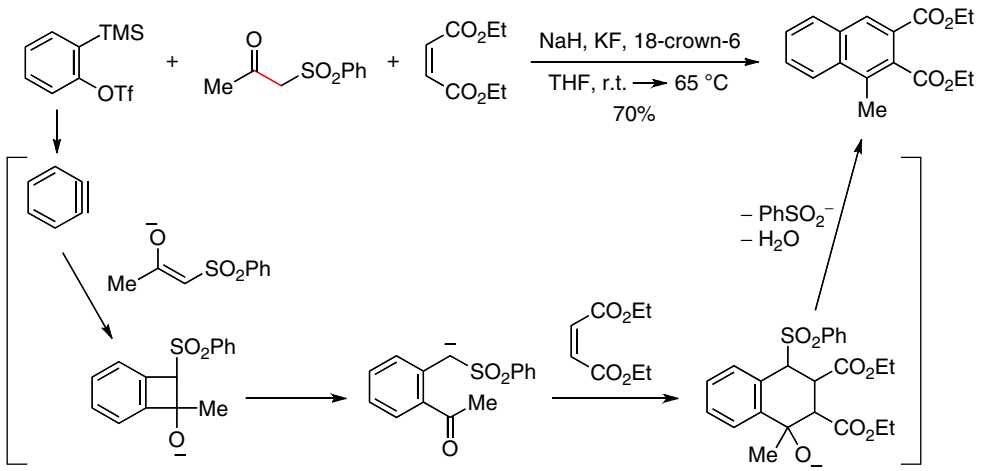
However, two molar amounts of arynes are preferentially coupled with *p*-tolylsulfonylacetonitrile or malononitrile through the insertion into the C(methylene)–C(cyano) and the C(methylene)–H bonds.[168] The reaction of 3-methoxybenzyne occurs with perfect regioselectivity, where the methine carbon is connected to the *meta*-positions of each methoxy moiety. Based on the reaction pathway for the insertion into β-ketoesters (**Scheme 44**), formation of the 2:1 coupling reaction products from arynes and above nitriles can be rationalized by supposing nucleophilic attack of intermediary benzyl anion **49** to a second aryne (**Scheme 48**).

Since the key for the successful insertion reaction is smooth formation of a carbanionic species [$(EWG)_2RC^-$] via rapid deprotonation induced by two EWGs, the use of another molecular scaffold having a C–H moiety of suitable acidity has resulted in a new C–C bond cleavage reaction. Thus, treatment of arynes with 9-fluorenyl ketones leads to facile insertion into the C(methine)–C(carbonyl) bond to give the acylfluorenylation products,[169] where formation of the key carbanionic species is facilitated by its aromatic stabilization (**Scheme 49**), and furthermore arynes are also inserted into various benzyl trifluoromethyl ketones (**Scheme 50**).[170] The reaction with trifluoromethyl mesitylmethyl ketone gives (*Z*)-*O*-arylation product **51** solely, which is attributable to stereoselective formation of enolate **50**, and exclusive production of benzocyclobutenol **52** by use of trifluoromethyl phenethyl ketone suggests concerted nature of [2 + 2] cycloaddition (see Section 4.09.3.2.5).

The insertion reaction into a C–C bond can be carried out using aryl halides as aryne precursors under basic conditions as well (see Section 4.09.2.1.1), and arylacetonitriles are frequently the substrates of choice.[171–173] Besides usual arynes, those bearing such an acidic substituent as carboxy[174] or hydroxy[175] smoothly participate in the insertion into the C(methylene)–C(cyano) bond of arylacetonitriles to give *ortho*-(arylmethyl)benzonitrile derivatives in good yield (**Scheme 51**). In the case of 3-thienylacetonitrile, intermediate **53**, generated via a formal [2 + 2] cycloaddition between an aryne and a lithiated acetonitrile, further undergoes an intramolecular cyclization to afford polycyclic compound **54** (**Scheme 52**).[176]

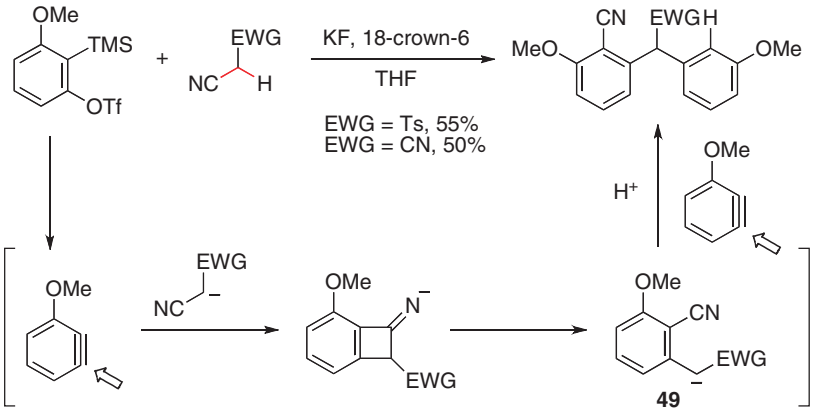


Scheme 46

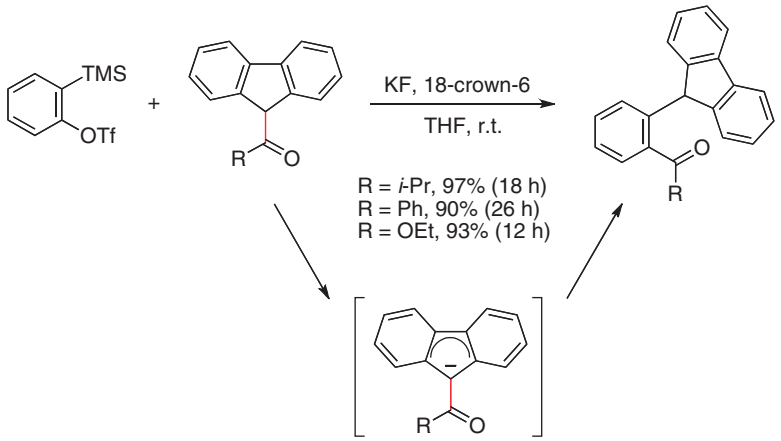


Scheme 47

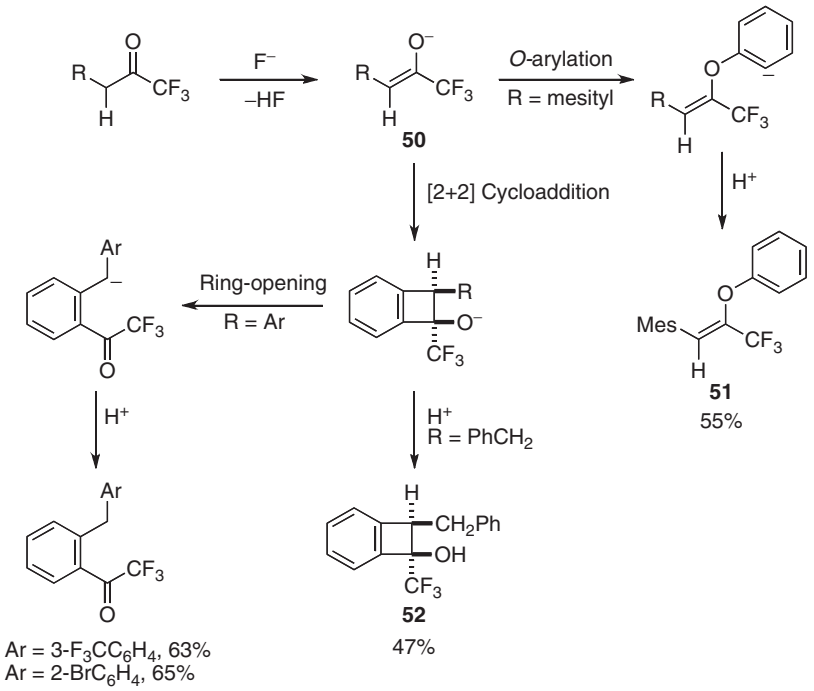
A dianion of crotonamide reacts with an aryne to provide a simple insertion product (**55**), whereas that of crotonic acid produces a 2-naphthol derivative (**56**) by a 6-*exo-trig* cyclization (Scheme 53).[177] In addition, arynes are inserted into an enolate of dialkyl malonate or 2-methylcyclopentanone to furnish homophthalate **57** or α-benzosuberone **58**, and the method is utilized for total synthesis of dynemicin A (**59**),[178] fredericamycin A (**60**),[179] angiogenesis inhibitor NM-3 (**61**),[180] or salvilenone (**62**)[181] (Scheme 54).



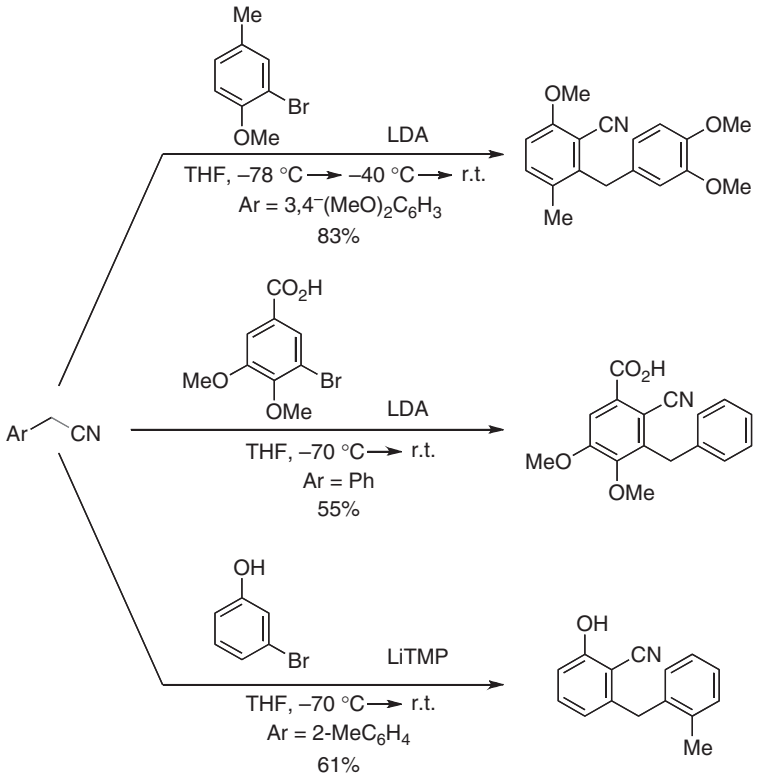
Scheme 48



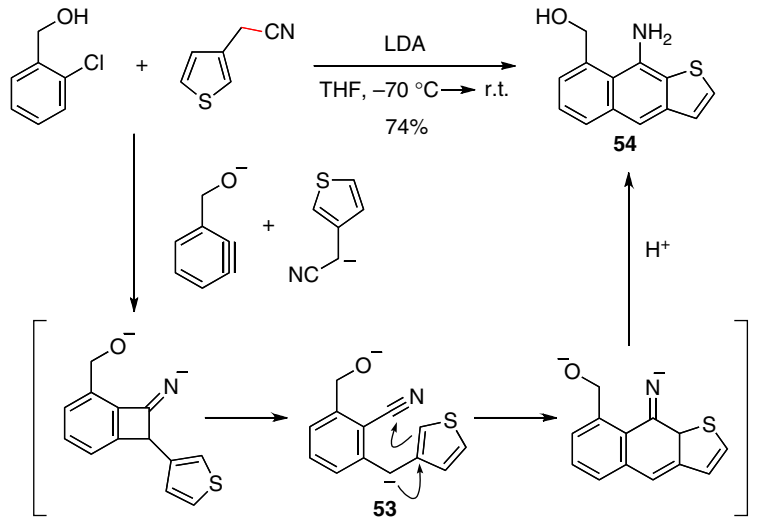
Scheme 49



Scheme 50



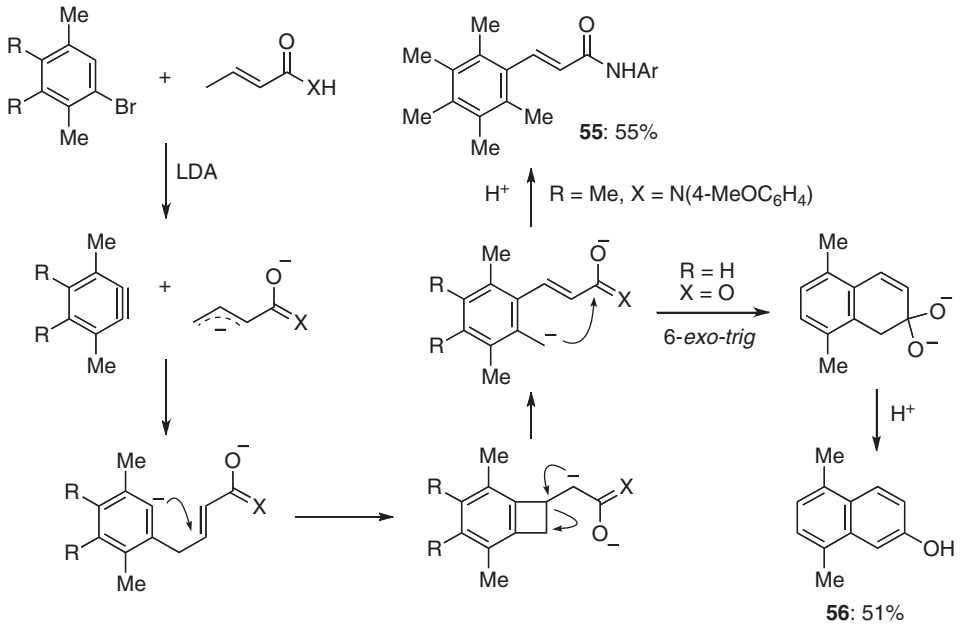
Scheme 51



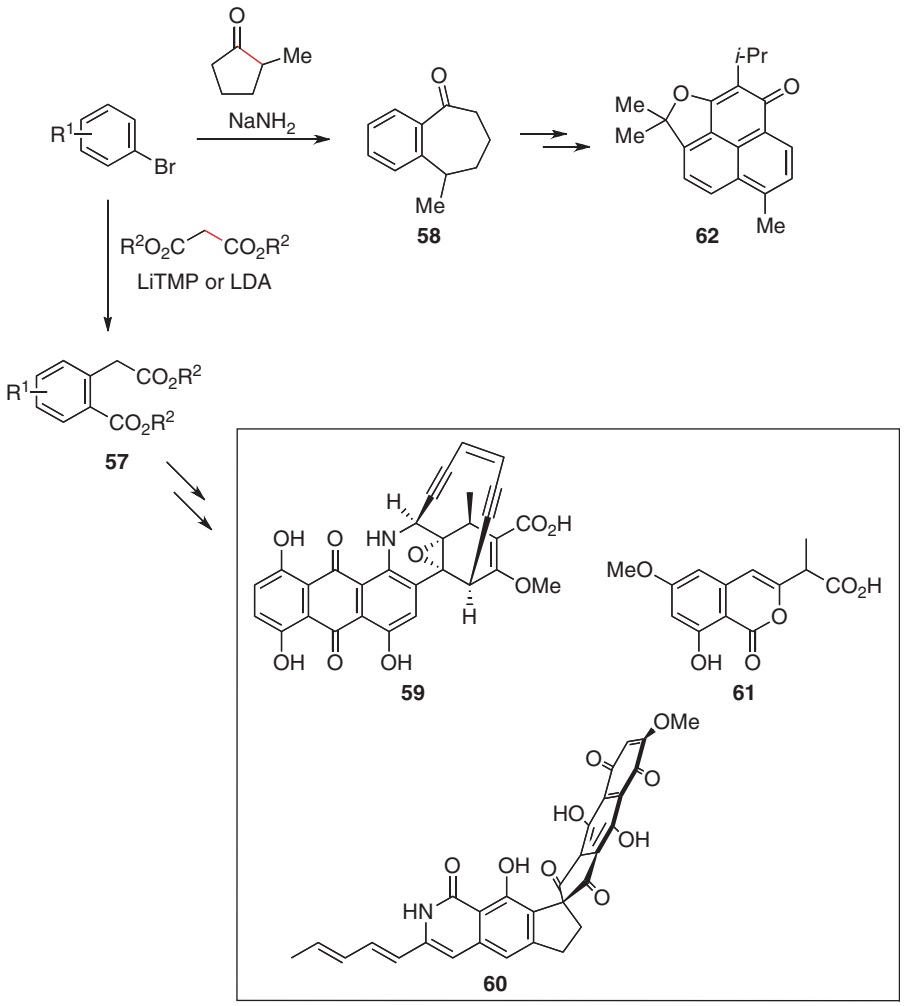
Scheme 52

4.09.3.2.3 1,n-Cycloaddition

Lithiated 3-cyanophthalides act as convenient 1,4-dipole equivalents toward arynes to afford aryne annulation products, anthraquinone derivatives in a straightforward manner. In addition to usual arynes,[182] 3,4-pyridyne,[183] 3,4-quinolyne,[183] and 2,3-didehydrobiphenylene[184] smoothly take part in the reaction (Scheme 55), and the wide applicability of the method allows

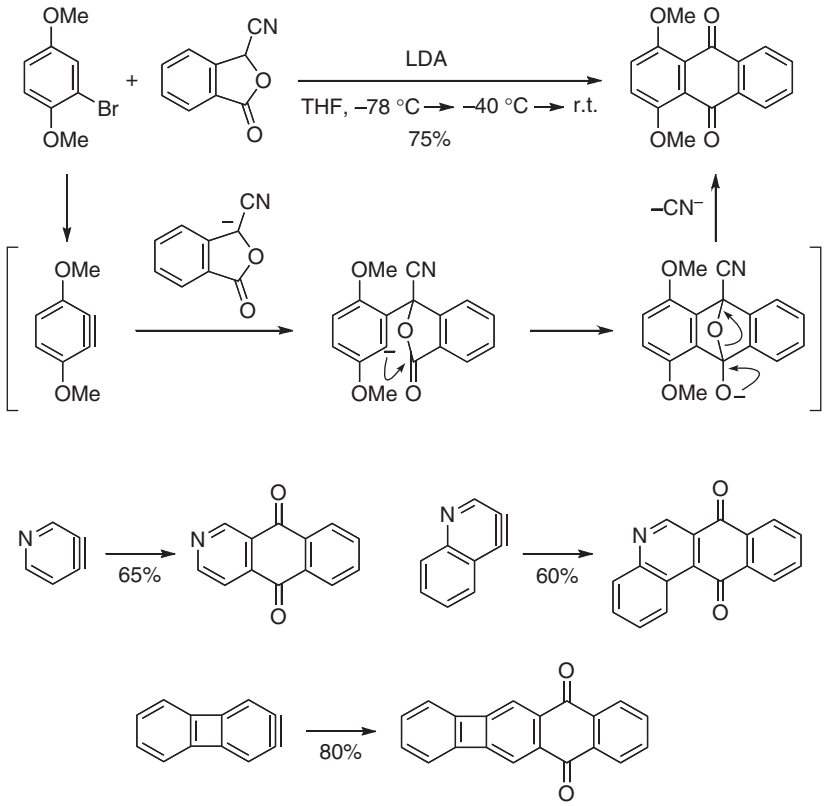


Scheme 53

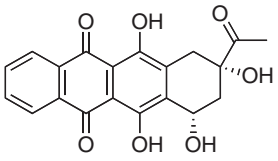


Scheme 54

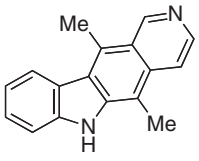
efficacious access to such biologically active compounds as 4-demethoxydaunomycinone (**63**),[185] ellipticine (**64**),[186] morindaparvin A (**65**),[187] and mumbaistatin analog (**66**).[188]



Scheme 55



63



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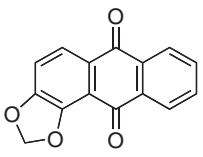
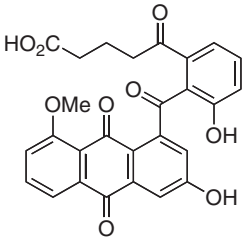


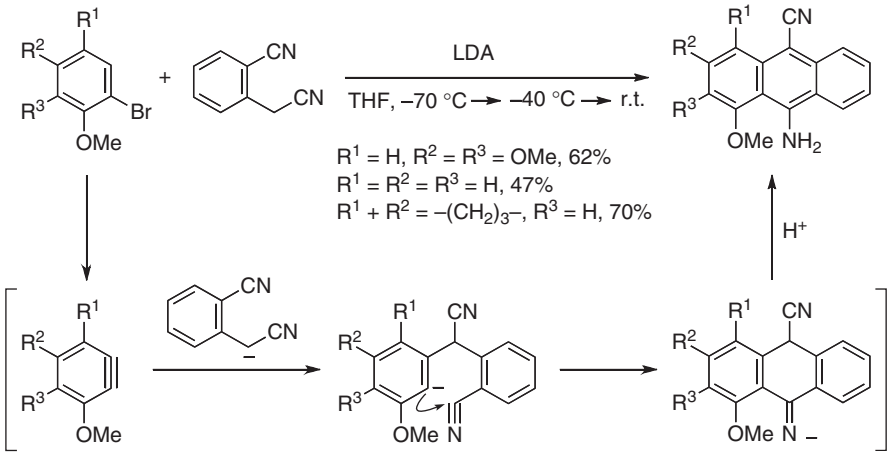
65



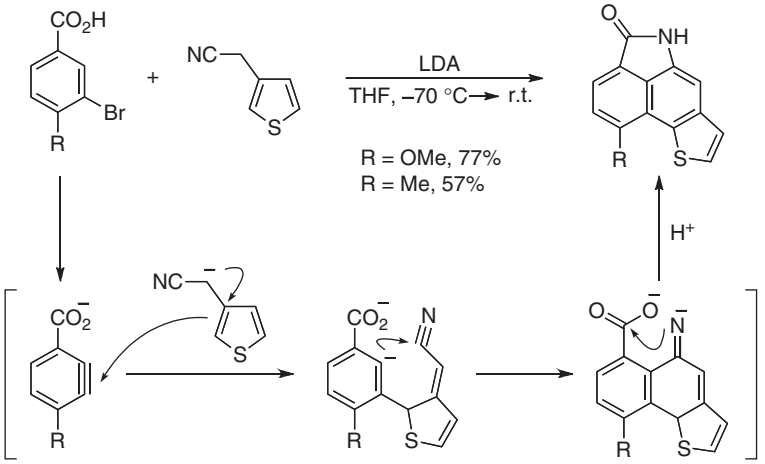
66

Construction of benzo-annulated six-membered ring has also been accomplished by the use of α-cyano-*ortho*-tolunitriles (Scheme 56),[173,189] 3-thienylacetonitrile (Scheme 57),[190] or benzocyclobutenols[191,192] under the similar reaction conditions. In the latter case, lithiated *ortho*-tolualdehydes, tautomers of benzocyclobutenoxides serve as 1,4-dipole equivalents (Scheme 58). A reaction of lithiated benzyl nitriles[193,194] or ethyl cyanoacetate[195] with 2 M amounts of arynes, which proceeds through insertion into a carbon–carbon bond (see Section 4.09.3.2.2) and the annulation with a second aryne, gives directly anthrone imines or 10-hydroxy-9-anthracenecarbonitriles (Scheme 59). Furthermore, extension of the annulation method to 1,4-dipole

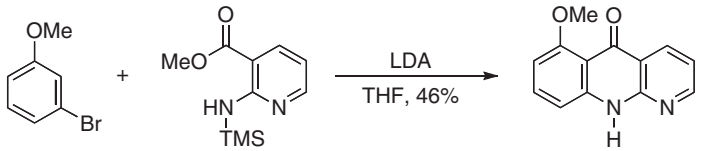
equivalents bearing an amino substituent as a nucleophilic moiety provides a convenient route to diverse six-membered *N*-heterocycles (equation 14).[39,196]



Scheme 56



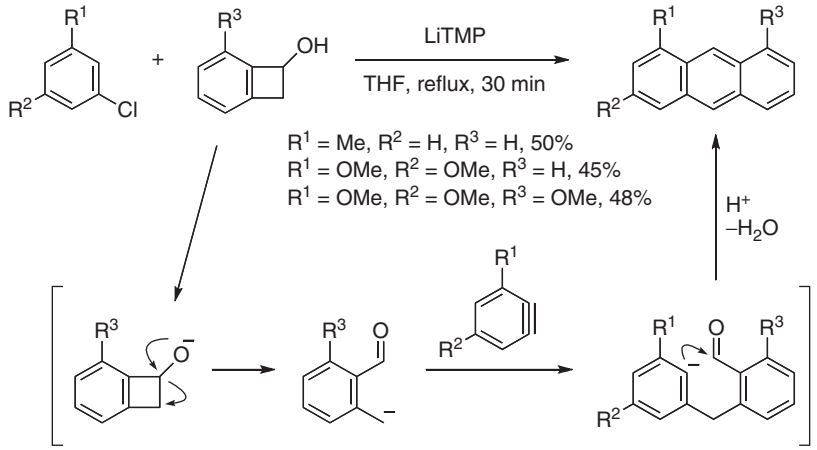
Scheme 57



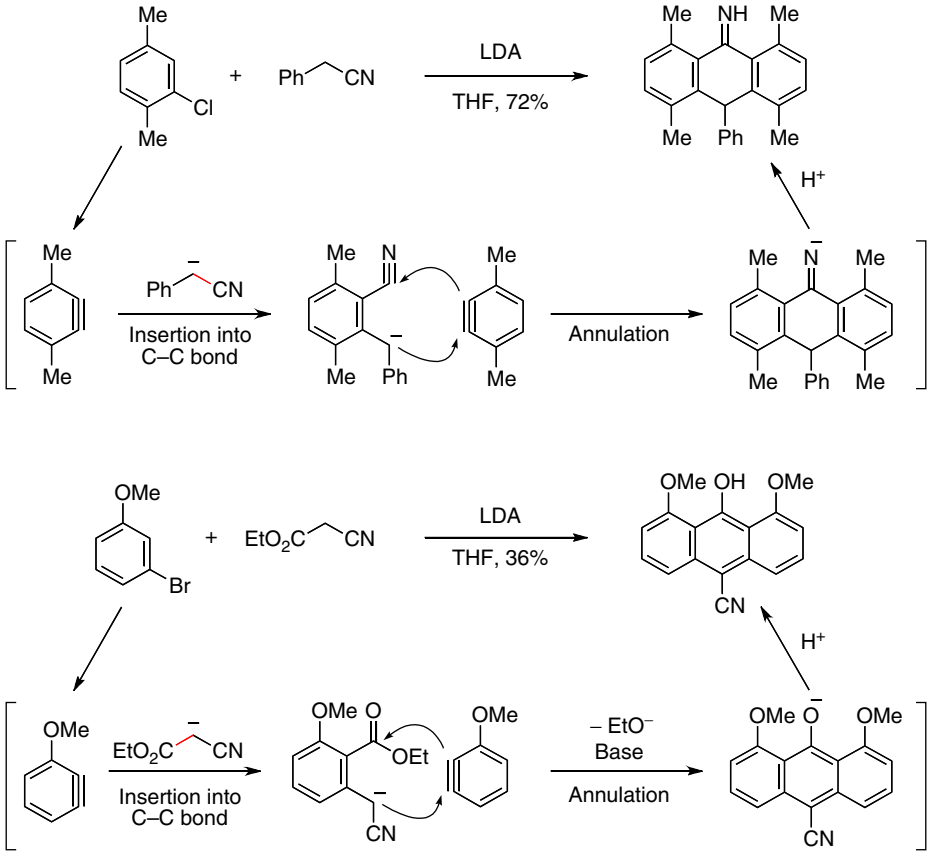
(14)

The versatility of the annulation method has been further improved by employing 2-(trimethylsilyl)aryl triflates as an aryne precursor: variously substituted xanthones **67**, thioxanthones **68**, and acridones **69** are facilely available from benzoates having a nucleophilic heteroatom (*O*, *S*, or *N*) at the *ortho*-position (**Scheme 60**),[197,198] and replacement of the electrophilic ester moiety into acyl,[199] formyl,[200] or electron-deficient alkenyl[201] group enhances the molecular diversity of the resulting six-membered heterocycles (**Scheme 61**).

In addition, treatment of *N*-acyl enamines with arynes produces isoquinolines via the formal [4 + 2] cycloaddition,[202,203] and this reaction has been employed in total synthesis of papaverine (**70**)[202] and (–)-quinocarcin (**71**)[204] (**Scheme 62**). Direct construction of benzo-annulated five-membered heterocyclic skeletons is also feasible depending on the aryne annulation using indole 2-carboxylates (**72**),[205,206] 2-oxo-2-(arylamino)acetates (**73**),[207] amino acid esters (**74**),[208] and *N*-carbamoyl dehydroalanine esters (**75**)[202] as 1,3-dipole equivalents (**Scheme 63**).



Scheme 58

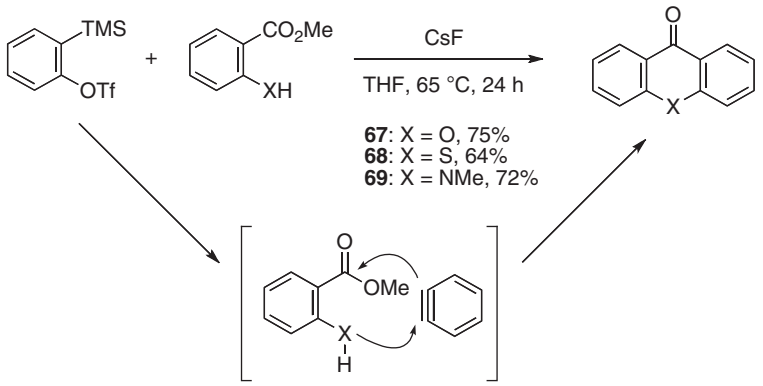


Scheme 59

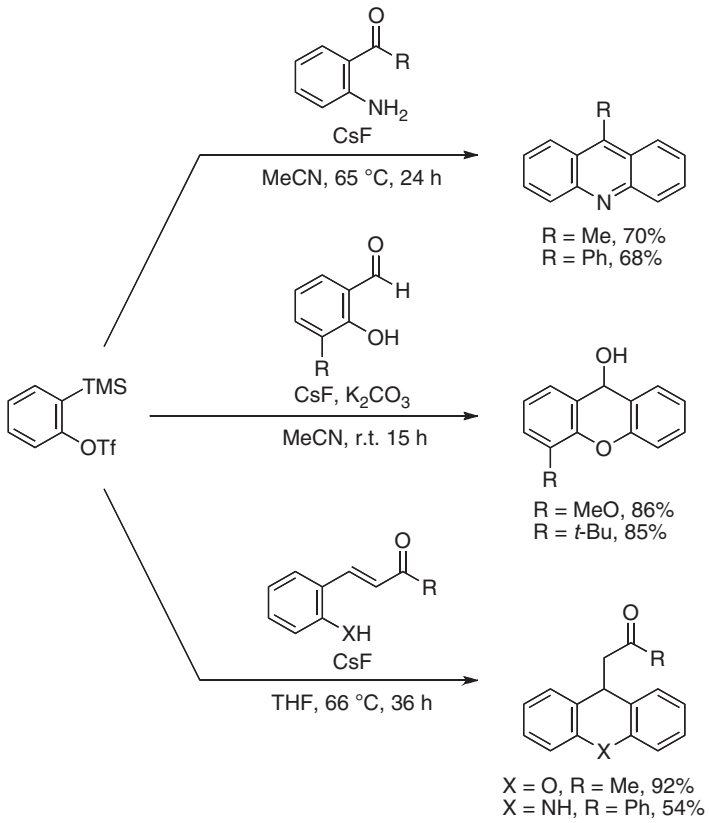
The formal [3 + 2] cycloaddition can be applied to one-step synthesis of benzofurans (from iodonium ylides)[209] and indoles (from azidoacrylates).[210] Although oxygen (**76**) and nitrogen (**77**) anions have been reported to be a nucleophilic site as described in Scheme 64, the regiochemical outcomes of 3-substituted arynes cannot be rationally explained by the pathways, and thus other mechanisms may be operative in these cases.

4.09.3.2.4 Multicomponent coupling

Arynes are utilizable as relay species in a multicomponent coupling with nucleophiles and electrophiles, allowing dual functionalization of the C–C triple bond in a straightforward manner. Various types of multicomponent coupling have been hitherto



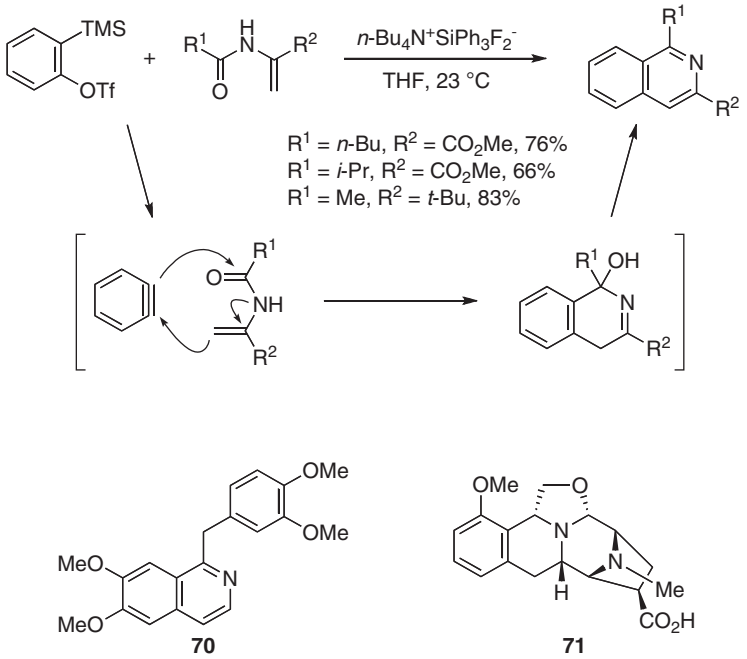
Scheme 60



Scheme 61

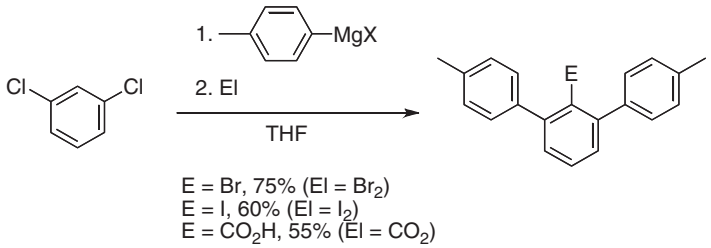
developed under basic or neutral conditions because the multicomponent couplings would be much more attractive from a synthetic standpoint in gaining molecular complexity and diversity. Such highly basic organometallics as oraganolithium and Grignard reagents are frequently used as the nucleophiles toward arynes in the multicomponent coupling to give *ortho*-substituted arylmetal reagents as key intermediates, which are convertible into final products by treatment with electrophiles. For example, 2-arylphenylmagnesium halides (**78**), derived from arynes and arylmagnesium halides, are trapped by chlorodialkylphosphines to afford multicomponent coupling products, (dialkylphosphino)biaryls in one pot (**Scheme 65**),[211,212] which are potent ligands in the Pd-catalyzed Suzuki–Miyaura cross-coupling and Buchwald–Hartwig amination.

The use of 1,3-dichloro-2-iodobenzene or 1,3-dichlorobenzene as an aryne precursor enables twofold installation of *para*-tolylmagnesium bromide, which results in formation of 2′-substituted *meta*-terphenyls (equation 15),[213] and furthermore treatment of *ortho*-bromoiodoarenes with *n*-BuLi provides 2-bromo-2′-iodobiaryls, where the starting dihaloarenes act as the source of arynes, aryllithiums (nucleophile), and an iodine cation (electrophile) (**Scheme 66**).[214,215] Similarly,



Scheme 62

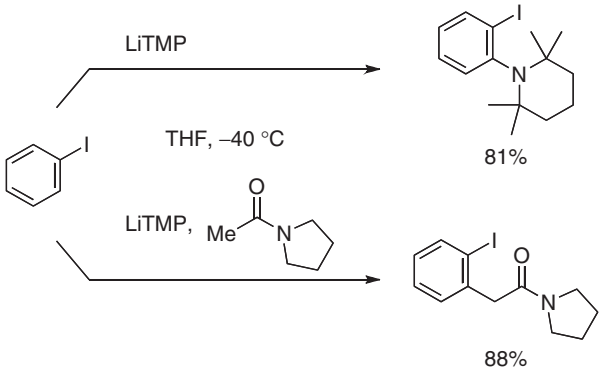
2-fluorophenyllithium generated from fluorobenzene and *t*-BuLi functions as a nucleophile and a benzyne precursor in the coupling with nitriles, giving phenanthridines through an intramolecular S_NAr reaction (Scheme 67).[216]



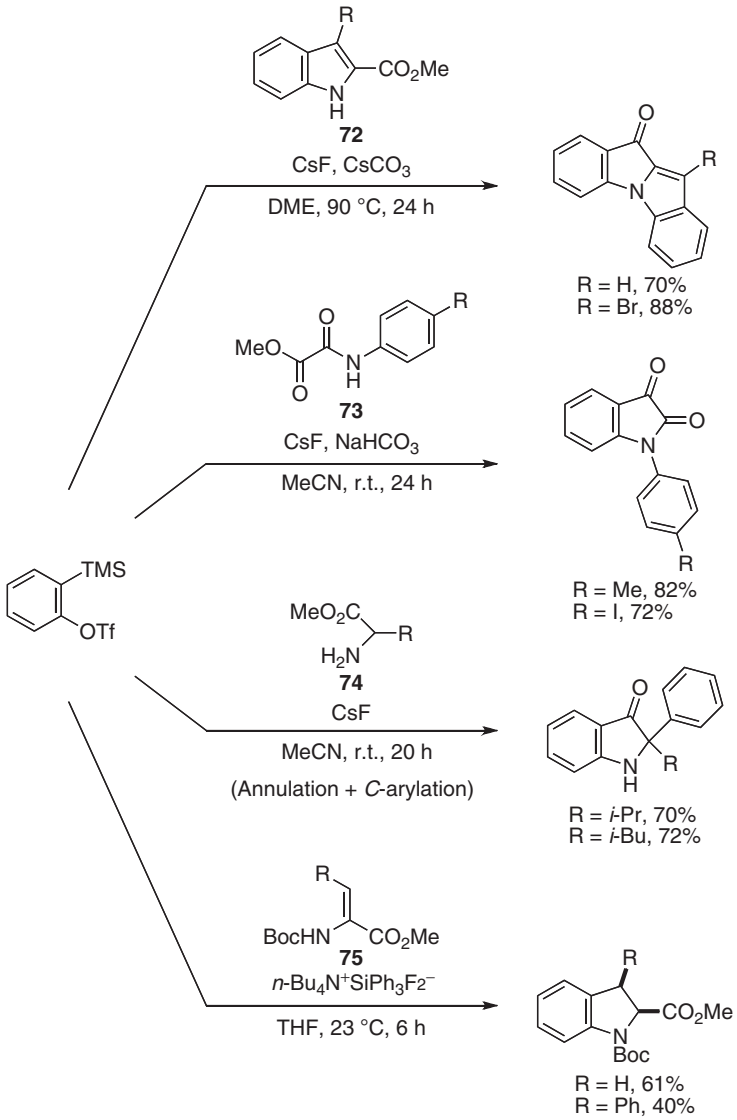
(15)

Allylmagnesium halides are efficient nucleophiles in the aryne multicomponent coupling with an aldehyde or CO_2, and these reactions have been utilized for total synthesis of clavilactone B (**79**, Scheme 68)[217] and dehydroaltenuene B (**80**, Scheme 69).[218] Functionalization of arynes with allylic nucleophiles is also possible by use of γ-silylallylcuprates, and arylcuprates thus formed are facilely trapped by carbon- or heteroatom-based electrophiles (Scheme 70).[219]

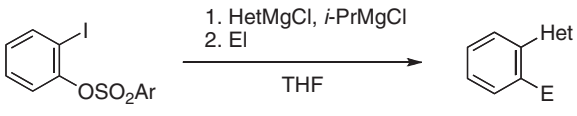
A lithium amide as well as a lithium enolate undergoes the reaction with arynes and an iodine cation equivalent (iodobenzene) to afford *ortho*-substituted iodoarenes (equation 16),[220] and heteronucleophile-based multicomponent coupling with wide substrate scope has been achieved by employing magnesium amides, thiolates, and selenides.[54,221,222]



(16)



Scheme 63

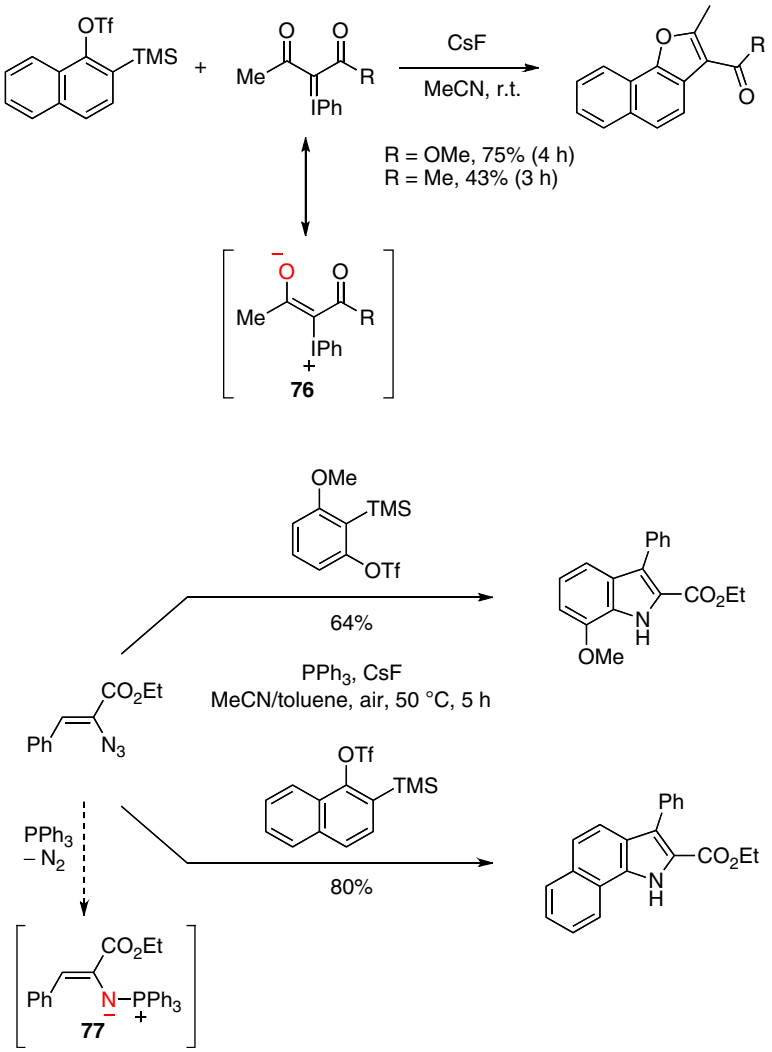


(17)

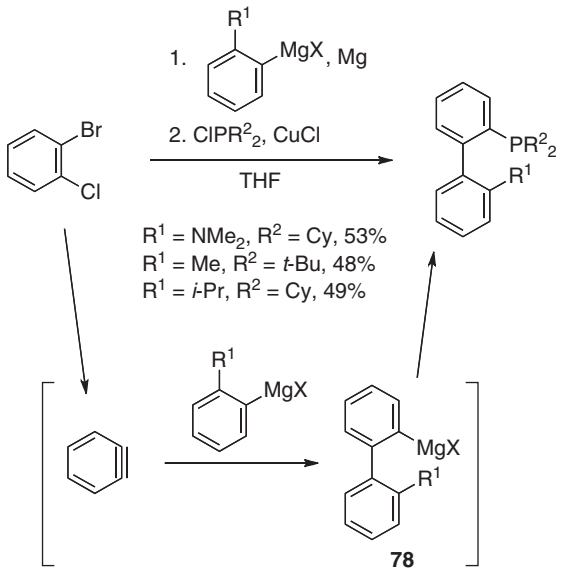
Ar = 4-ClC$_6$H$_4$

Het = PhMeN, E = allyl, 83% (EI = allylBr)
Het = 4-BrC$_6$H$_4$S, E = Bz, 88% (EI = BzCl)
Het = PhSe, E = CHO, 83% (EI = DMF)

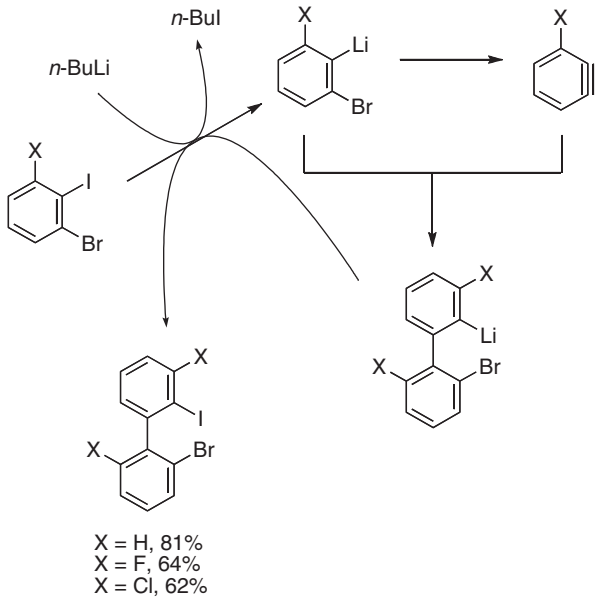
The reaction of arynes, isocyanides, and aldehydes under neutral conditions (see Section 4.09.2.2) produces benzo-annulated *O*-heterocycles, iminoisobenzofurans **81** in good yields.[223] As shown in Scheme 71, an initially formed zwitterion **82** from an aryne and an isocyanide reacts with an aldehyde to afford intermediate **83**, which is finally converted into the product by an intramolecular cyclization. Aldehydes can be replaced by ketones,[224] benzoquinones,[224] sulfonylimines,[225] esters[226] and electron-deficient alkynes,[226] leading to formation of the respective five-membered cyclic structures (equation 18), and moreover six-membered *N*,*O*-heterocycles are fabricated in the reaction with imines and CO_2 (Scheme 72).[227]



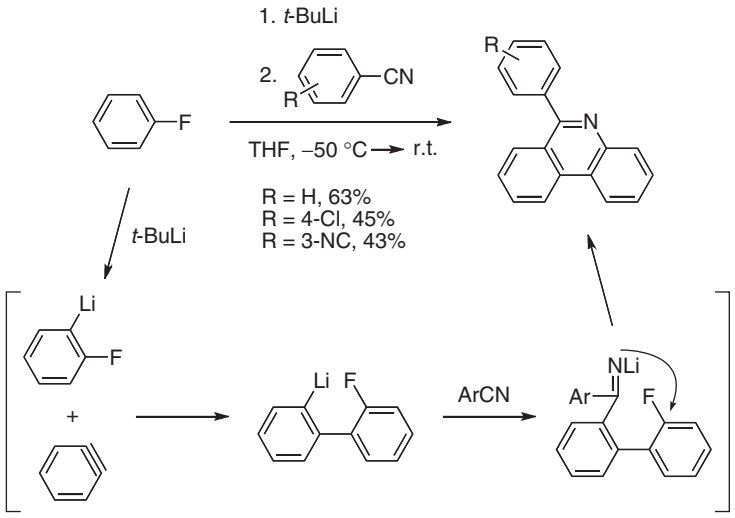
Scheme 64



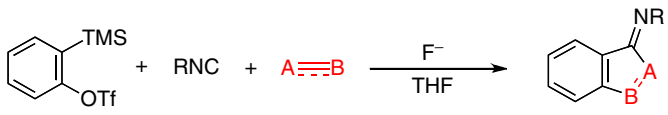
Scheme 65



Scheme 66



Scheme 67

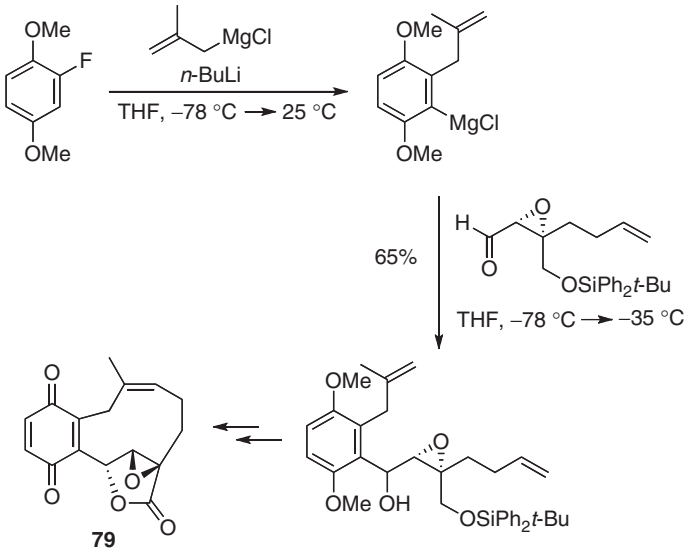


(18)

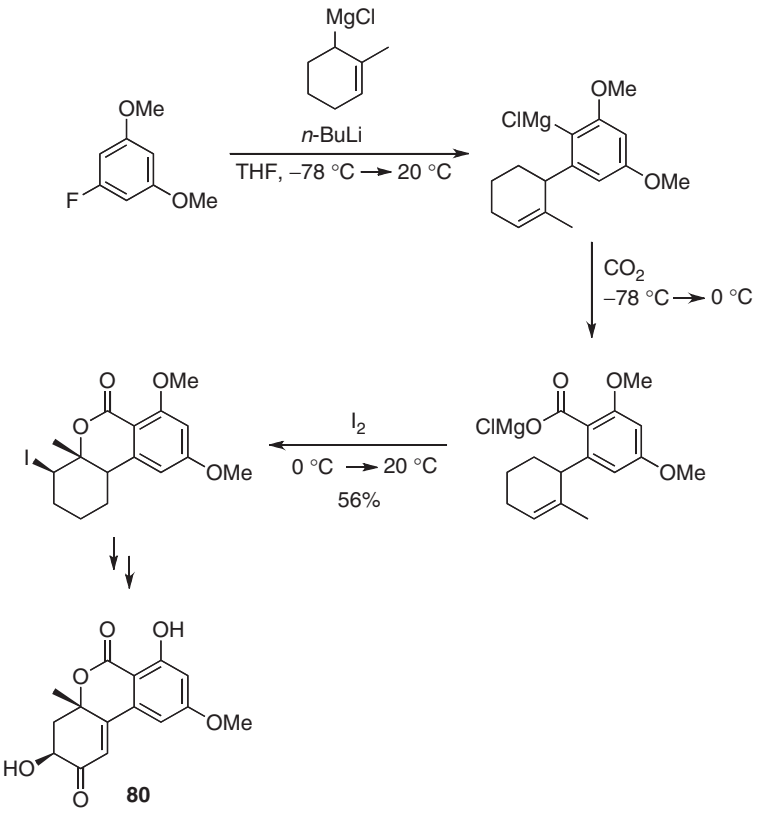
Benzoquinone Sulfonylimine

Isocyanide-derived zwitterion **82** can also be captured by alkynyl and perfluoroaryl bromides to give **84** and **85** (Scheme 73),[228] and the method allows the use of cyclic ethers including oxetanes and THF of less nucleophilicity, which are transformed into ring-opened products (Scheme 74). C–Br bond- and subsequent C–C bond-forming processes between carbanion **86** and nitrilium cation **87** (or oxonium cation **88**) rationally explain the product formation (Scheme 75). Synthetic utility of the reaction has been demonstrated by total synthesis of benzo[*b*]oxepine-based nonsteroidal estrogen (**89**) (Scheme 76).

Although one carbon end of arynes is protonated, the reaction with benzyl isocyanides and terminal alkynes provides a unique way of constructing pyridine and isoquinoline frameworks via a [4 + 2] cycloaddition between a second alkyne (or aryne) and allenyl imine intermediate **90** (Scheme 77).[229] Similar reactions using *N*-heteroaromatics (pyridine and isoquinoline)[230,231] or



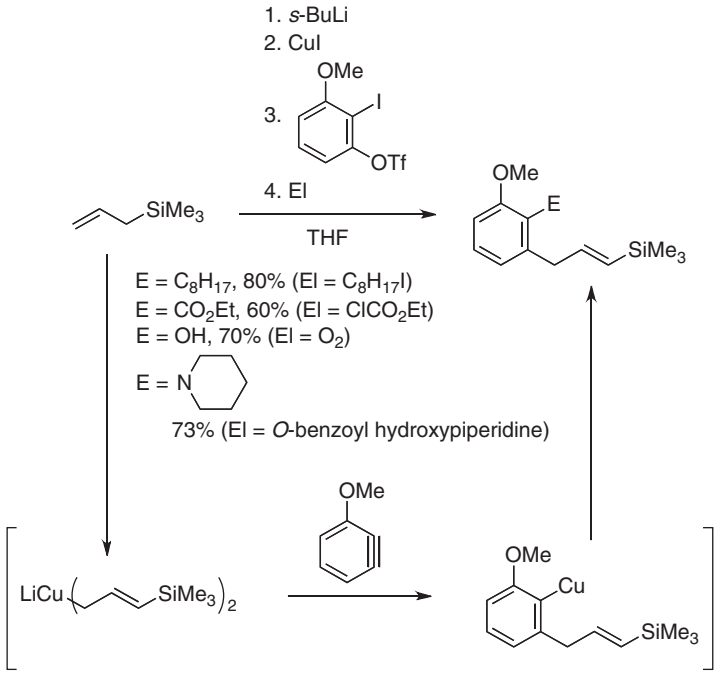
Scheme 68



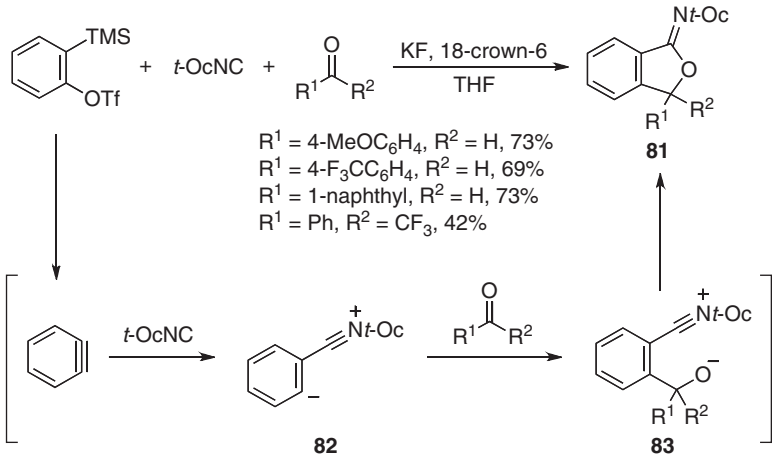
Scheme 69

cyclic ethers[232–234] as nucleophiles also readily occur in the presence of such protic electrophiles as nitriles, ketones, terminal alkynes, and chloroform (Scheme 78).

Arynes are smoothly coupled with aminosilanes and carbonyl compounds (or sulfonylimines) under the neutral conditions, enabling amino and hydroxymethyl (or aminomethyl) moieties to be incorporated into contiguous positions of aromatic rings (equation 19).[235,236] Secondary amines likewise undergo the coupling with arynes and CO_2 to give anthranilic acid derivatives (equation 20).[237] A multicomponent coupling involving arynes, pyridines, and α-bromocarbonyl compounds directly provides

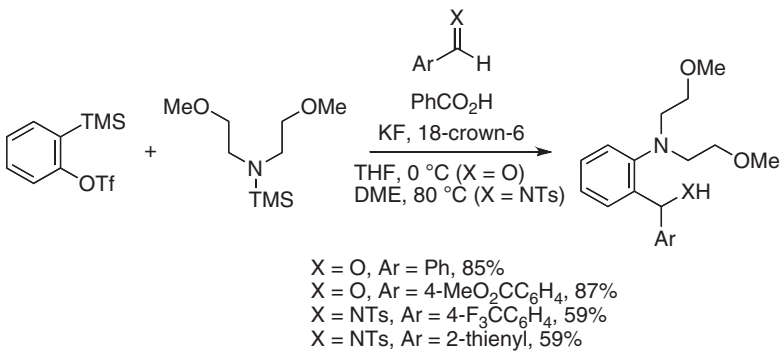


Scheme 70

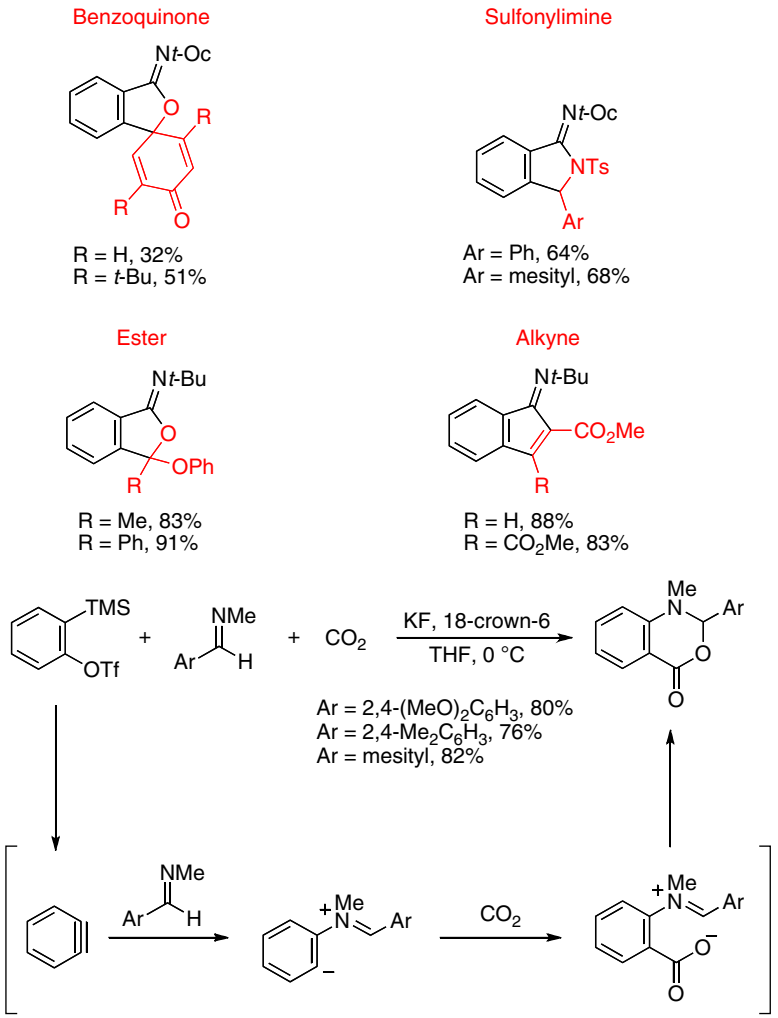


Scheme 71

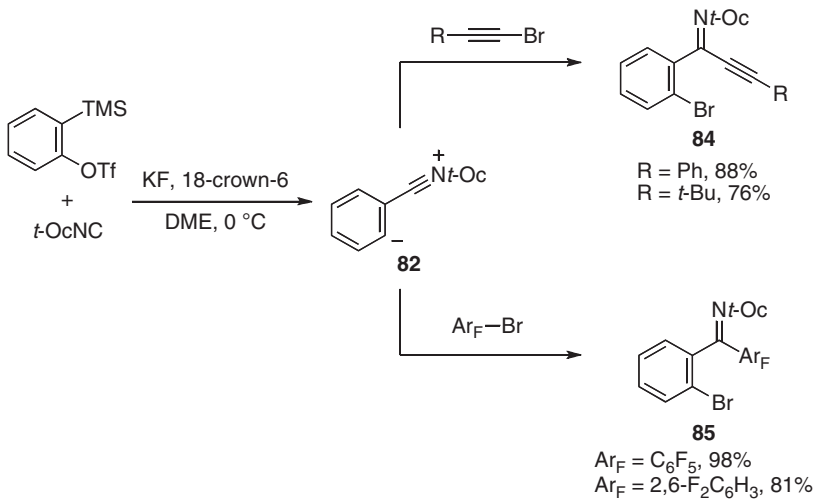
pyrido [2,1-a] isoindoles through a formal [3 + 2] cycloaddition between arynes and *in situ*-generated 1,3-dipoles (**91**) (Scheme 79).[238,239]



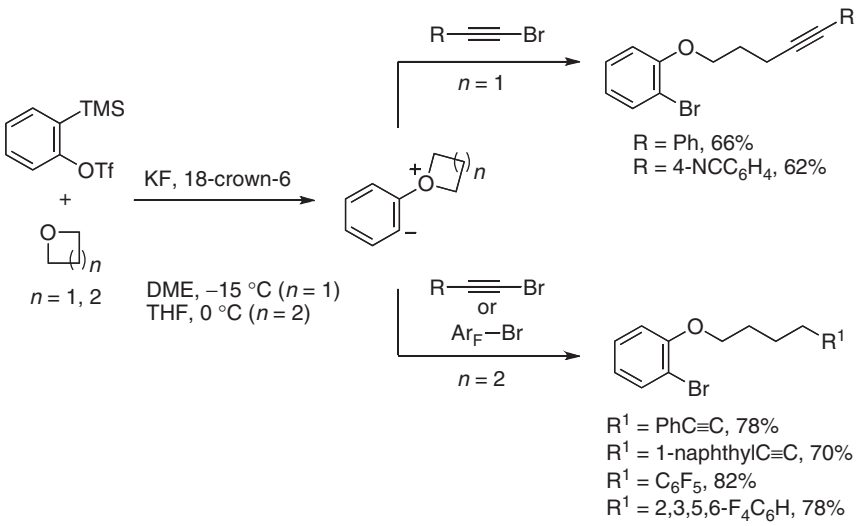
(19)



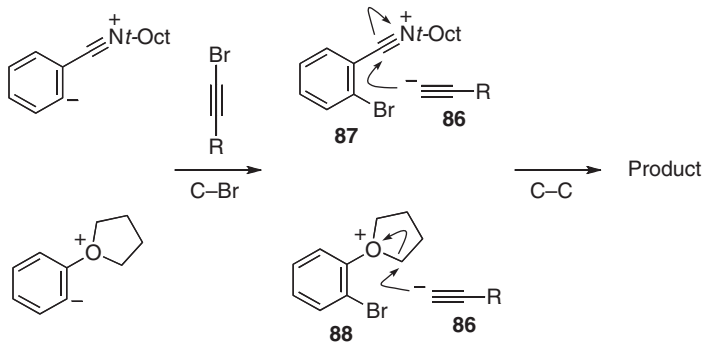
Scheme 72



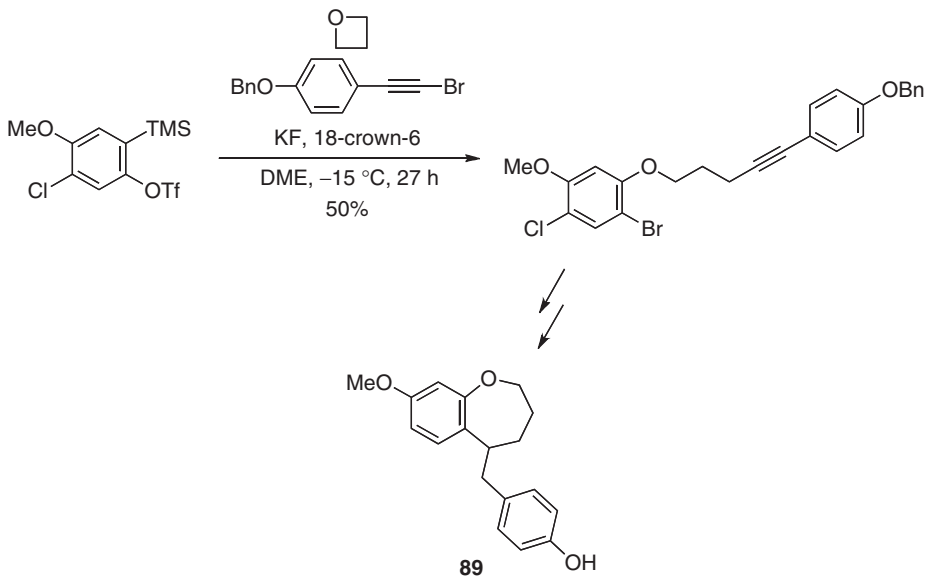
Scheme 73



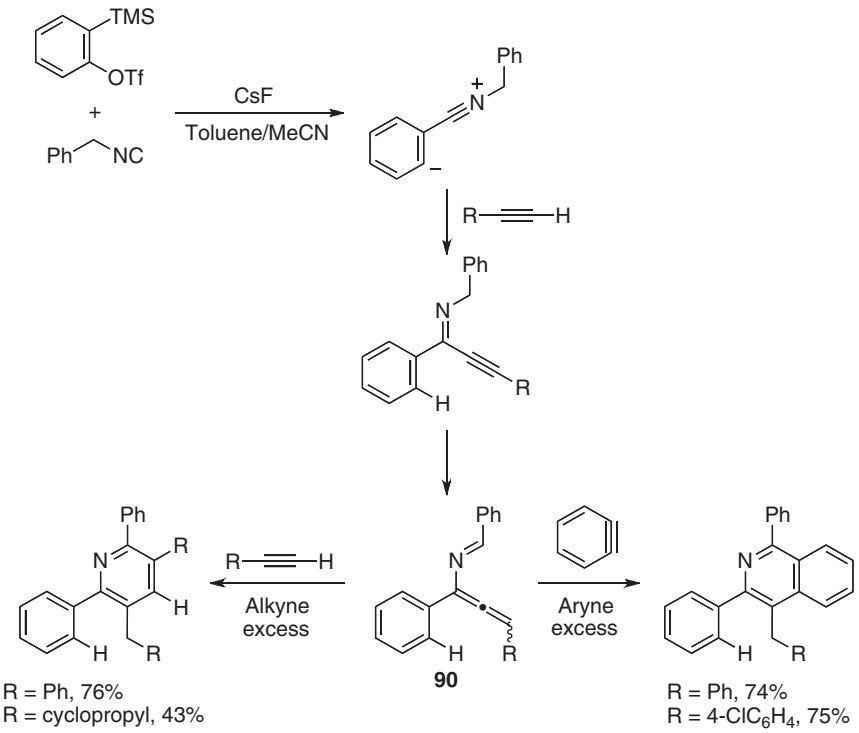
Scheme 74



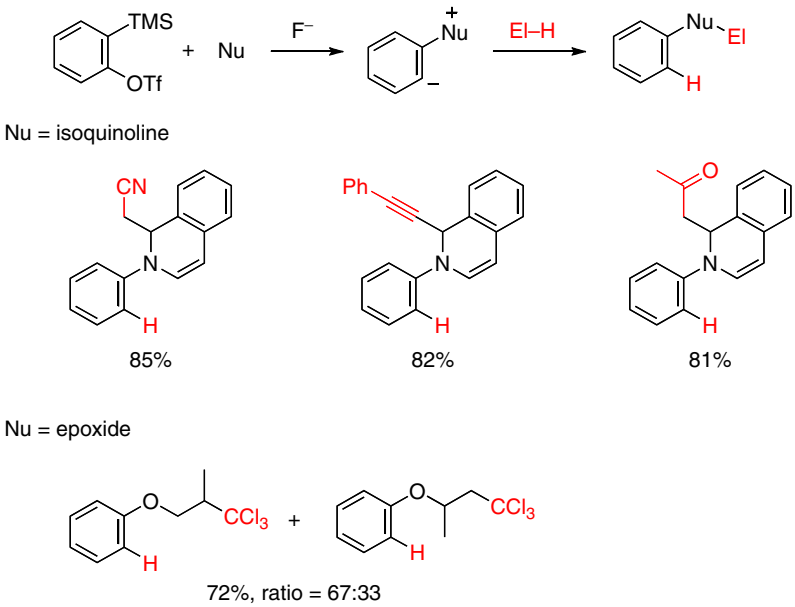
Scheme 75



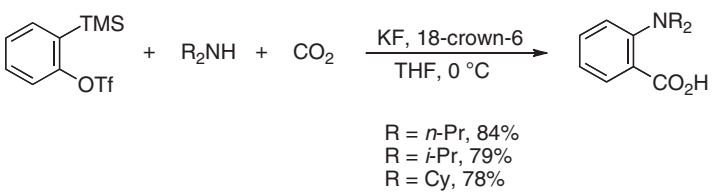
Scheme 76



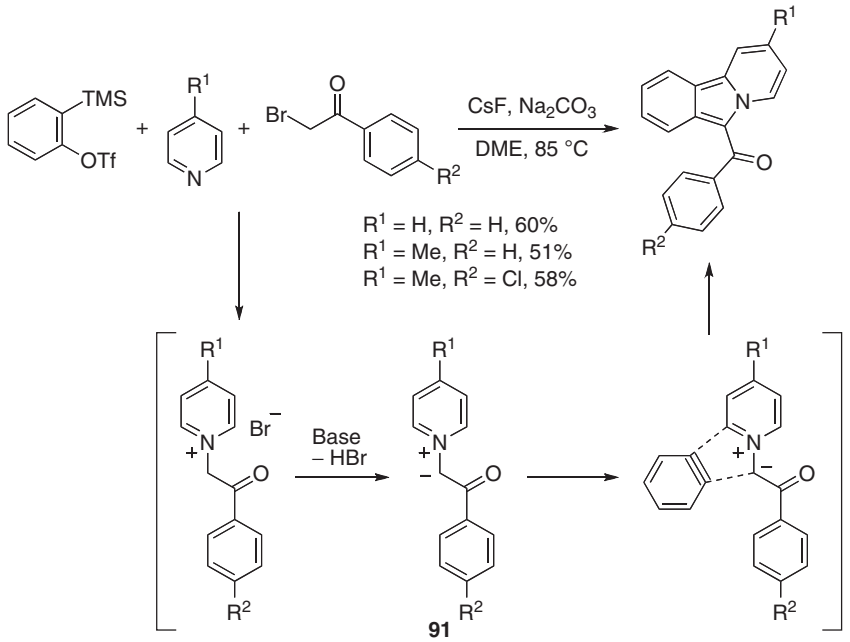
Scheme 77



Scheme 78



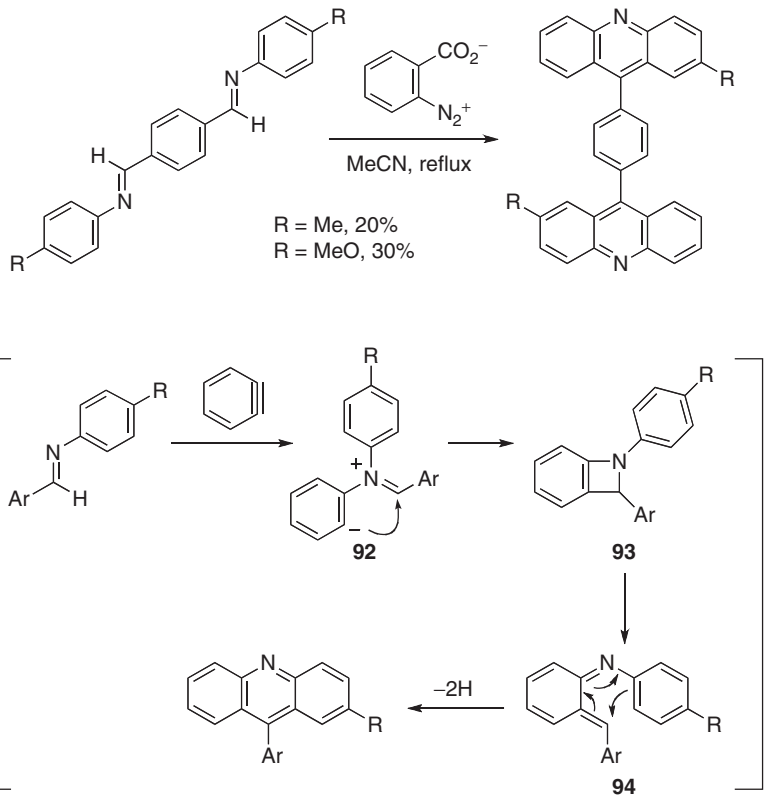
(20)



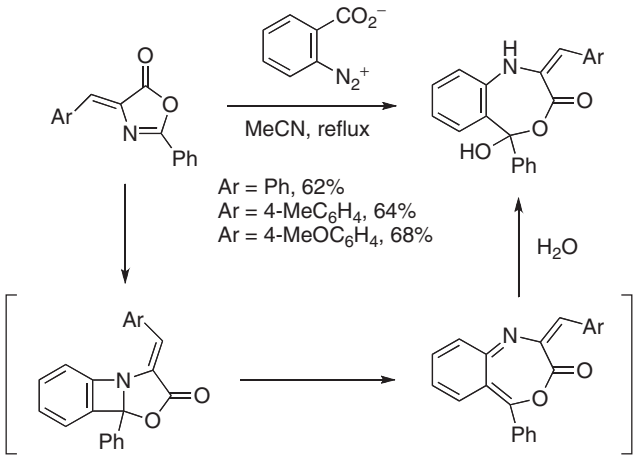
Scheme 79

4.09.3.2.5 [2 + 2] Cycloaddition

A carbon–nitrogen double bond of imines readily undergoes [2 + 2] cycloaddition with arynes probably via intermediary formation of zwitterion **92**, giving benzoazetines (**93**) straightforwardly. The resulting benzoazetines are susceptible to valence isomerization into aza-*ortho*-xylylenes (**94**), which furnish acridine derivatives by electrocyclization and aromatization (Scheme 80).[240,241] A similar reaction using oxazolones leads to the formation of benzoxazepine derivatives,[242] being attributable to addition of water to the aza-*ortho*-xylylene intermediates (Scheme 81).

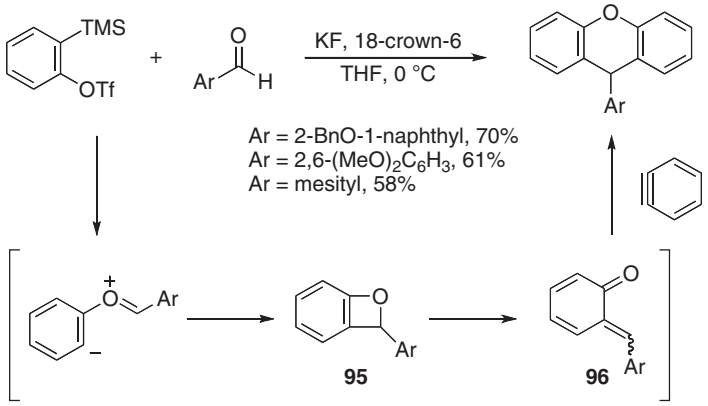


Scheme 80

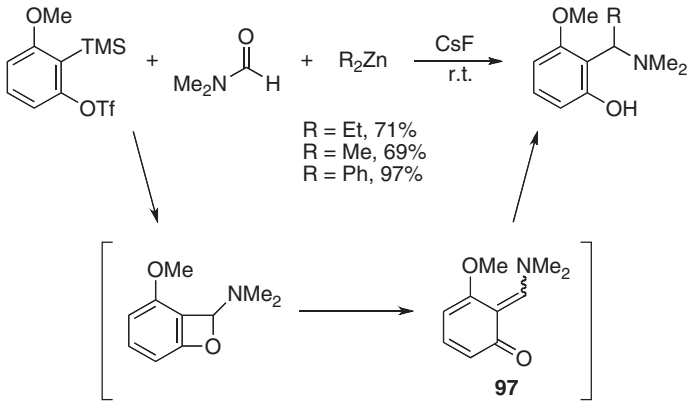


Scheme 81

The [2 + 2] cycloaddition with aldehydes smoothly proceeds to afford benzoxete **95** in a similar manner as above. Subsequent valence isomerization affords *ortho*-quinone methides (**96**), which further react with second arynes to give various xanthenes in one pot (Scheme 82).[243] A formyl moiety of *N*,*N*-dimethylformamide (DMF) is also transformable into *ortho*-quinone methides (**97**) via the [2 + 2] cycloaddition, and the resulting intermediates can be captured by organozinc reagents to provide *ortho*-hydroxybenzylamines (Scheme 83).[244] The DMF-derived *ortho*-quinone methides undergo formal [4 + 2] cycloaddition with

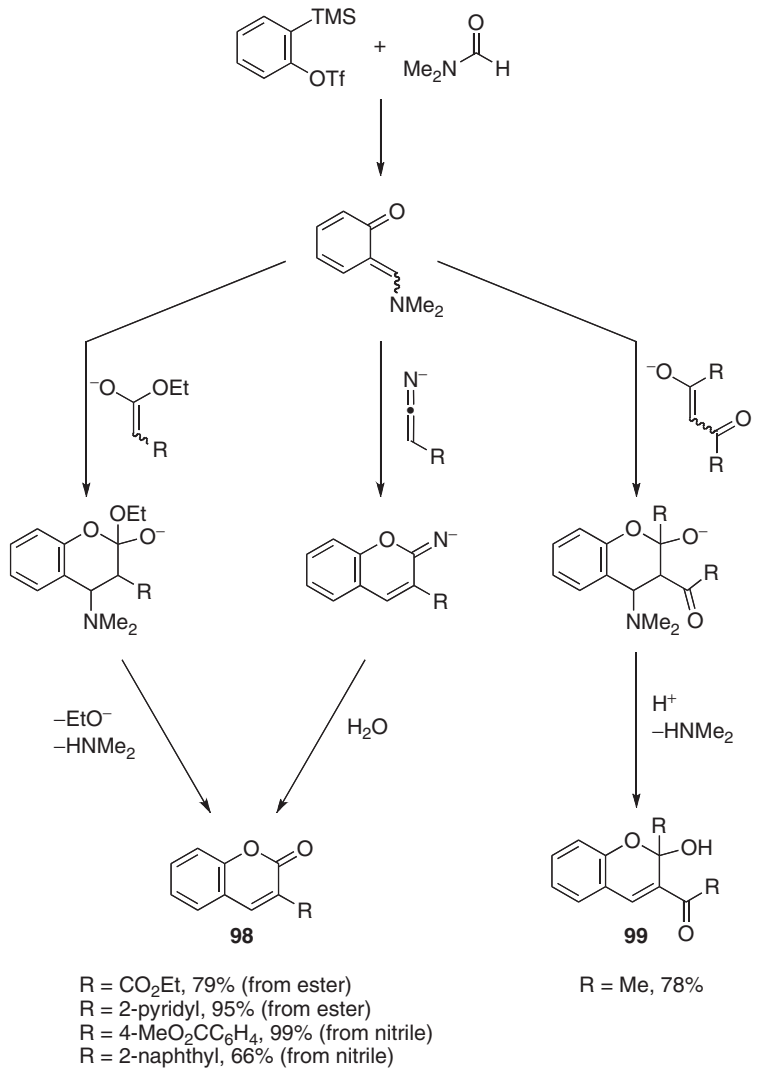


Scheme 82



Scheme 83

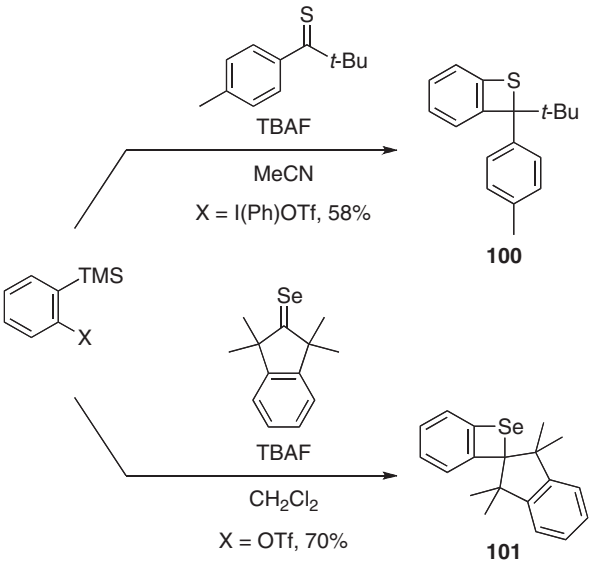
in situ-generated enolates (from malonates or β-diketones) or ketenimine anions (from arylacetonitriles), giving coumarins (**98**) and 2*H*-chromenes (**99**) in high yields (Scheme 84).[245,246]



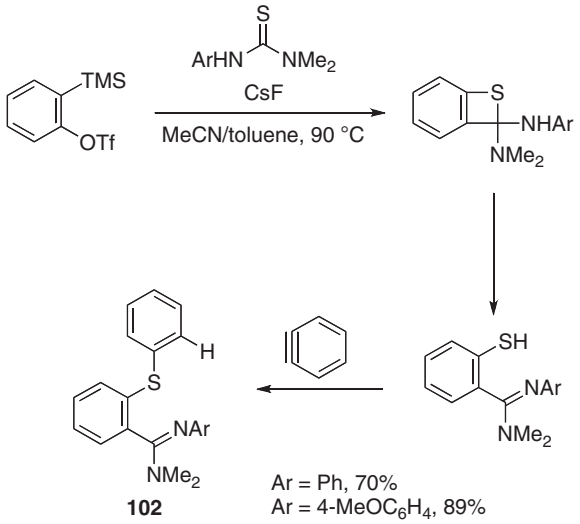
Scheme 84

In contrast to the above [2 + 2] cycloaddition, the reaction of sterically hindered thiones or selones with arynes produces stable four-membered cycloadducts, benzothietes (**100**),[94,247,248] and benzoselenetes (**101**)[249] (Scheme 85). However, benzothietes derived from thioureas easily suffer ring-opening to afford product **102** (Scheme 86).[250] The [2 + 2] cycloaddition with a P=N bond of λ^5-phosphazenes, where the nitrogen atom serves as a nucleophilic site toward arynes, has been also reported (Scheme 87).[251]

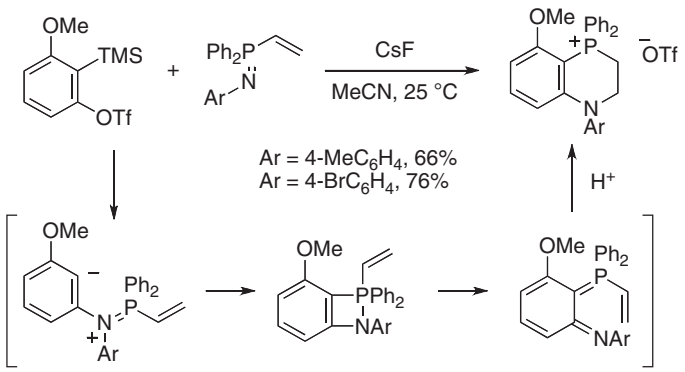
Extensive studies have been carried out on the direct synthesis of diverse benzocyclobutenes by the [2 + 2] cycloaddition of arynes with electron-rich alkenes including enolates,[191,192] ketene acetals,[252,253] and enamides,[254] which is closely related to the aryne insertion into a carbon–carbon bond (see Section 4.09.3.2.2). In particular, the reaction with ketene silyl acetals[50] has attracted considerable attention, since it is applicable to a synthesis of highly strained di- and tricyclobutabenzenes (Scheme 88).[255–257] The regioselectivity is generally high: an electron-rich carbon terminus of the ketene silyl acetals preferentially adds to a *meta*-position of 3-alkoxybenzynes and cyclobutane-fused arynes (equation 21, see Section 4.09.3.1.1).[105,258] Moreover, *E*/*Z* ratios of the ketene silyl acetals are reflected completely on *trans*/*cis* ratios of the products, showing the stereospecific nature of the [2 + 2] cycloaddition (equation 22).[259] Valence isomers of the benzocyclobutenes obtained by the [2 + 2] cycloaddition, *ortho*-quinodimethanes (**103**), are utilized for production of various polycyclic compounds including berbine derivatives (**104**) through the [4 + 2] cycloaddition with dienophiles (Scheme 89).[260]



Scheme 85

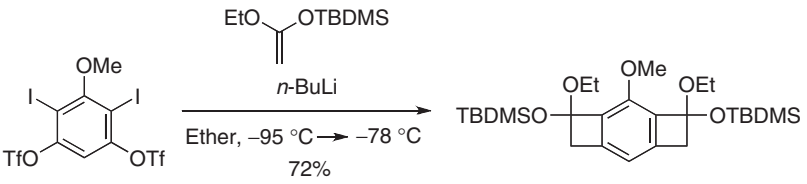


Scheme 86

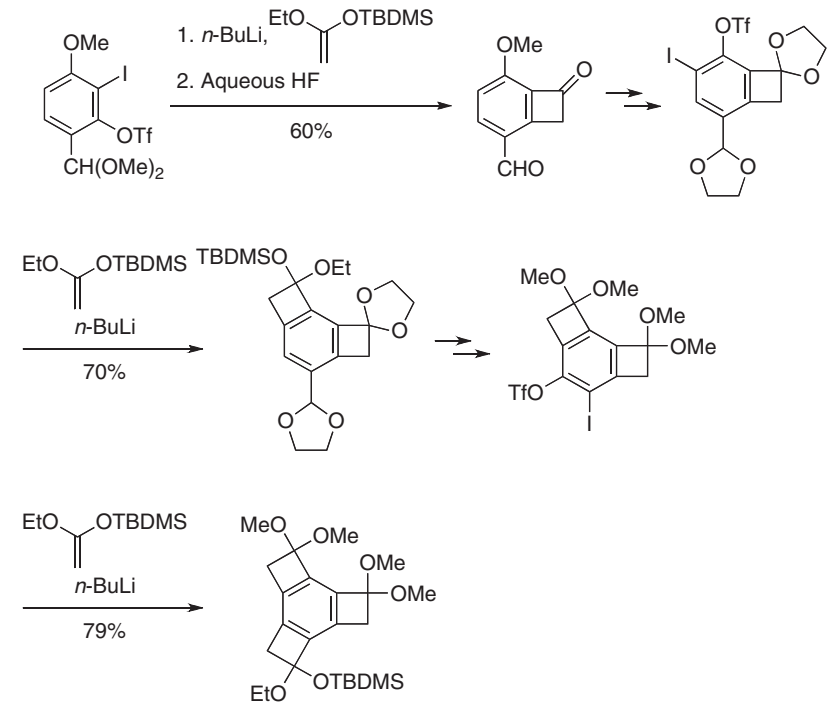


Scheme 87

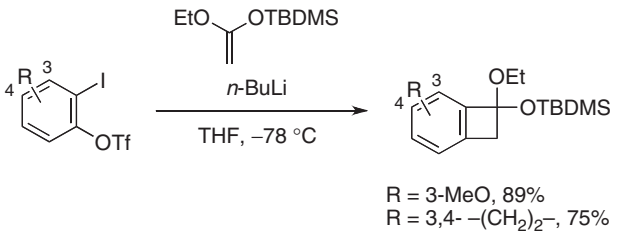
Dicyclobutabenzene



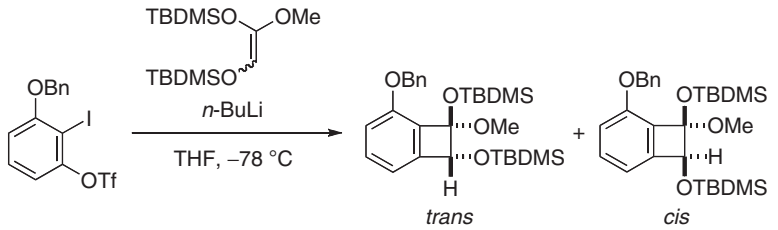
Tricyclobutabenzene



Scheme 88

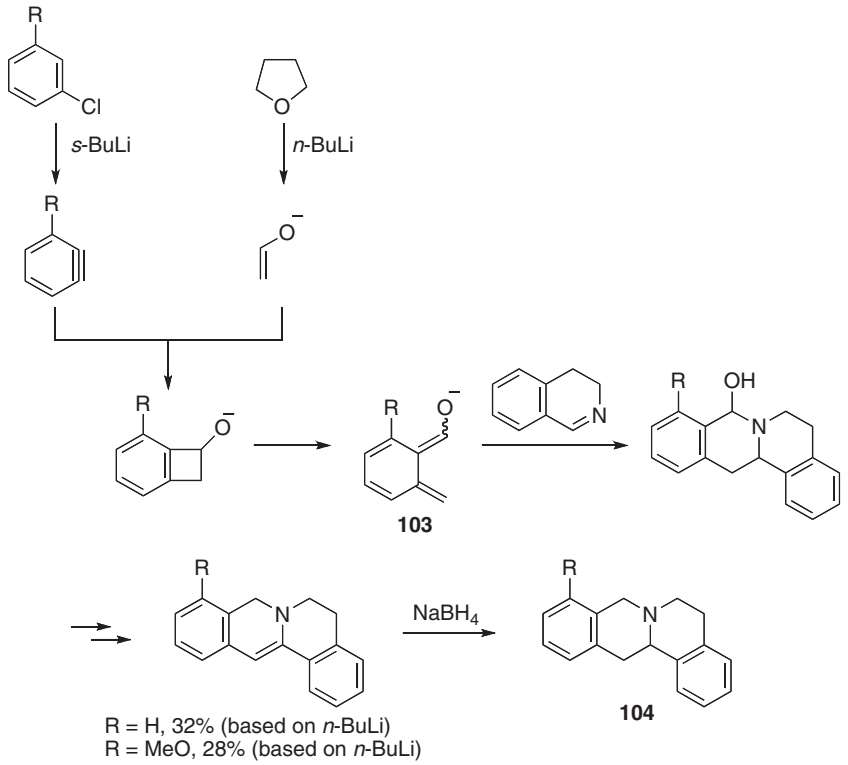


(21)



(22)

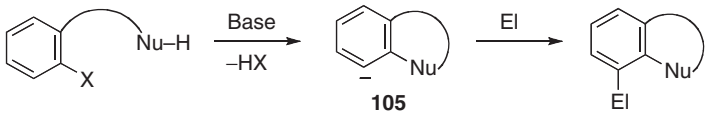
E/*Z* ratio of ketene silyl acetal	yield (%)	*trans*/*cis*
90/10	81	90/10
47/53	80	46/54
3/97	81	3/97



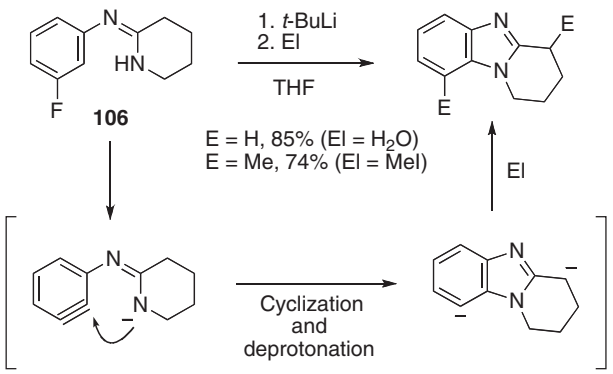
Scheme 89

4.09.3.2.6 Intramolecular reaction

An intramolecular cyclization of aryne-tethered nucleophiles has attracted much attention as a powerful method for constructing benzo-annulated cyclic skeletons. Because of higher availability of aryl halides compared with other aryne precursors, deprotonation method is mostly used in the cyclization (see Section 4.09.2.1.1), and thus a key intermediate under the basic conditions is aryl anionic species **105** which can be trapped by various electrophiles, enhancing molecular diversity of the resulting ring-closing products (Scheme 90). As depicted in Scheme 91, amidine **106** is smoothly convertible into cyclized products, benzimidazoles in

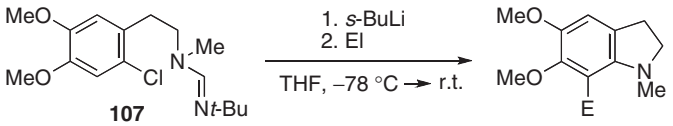


Scheme 90



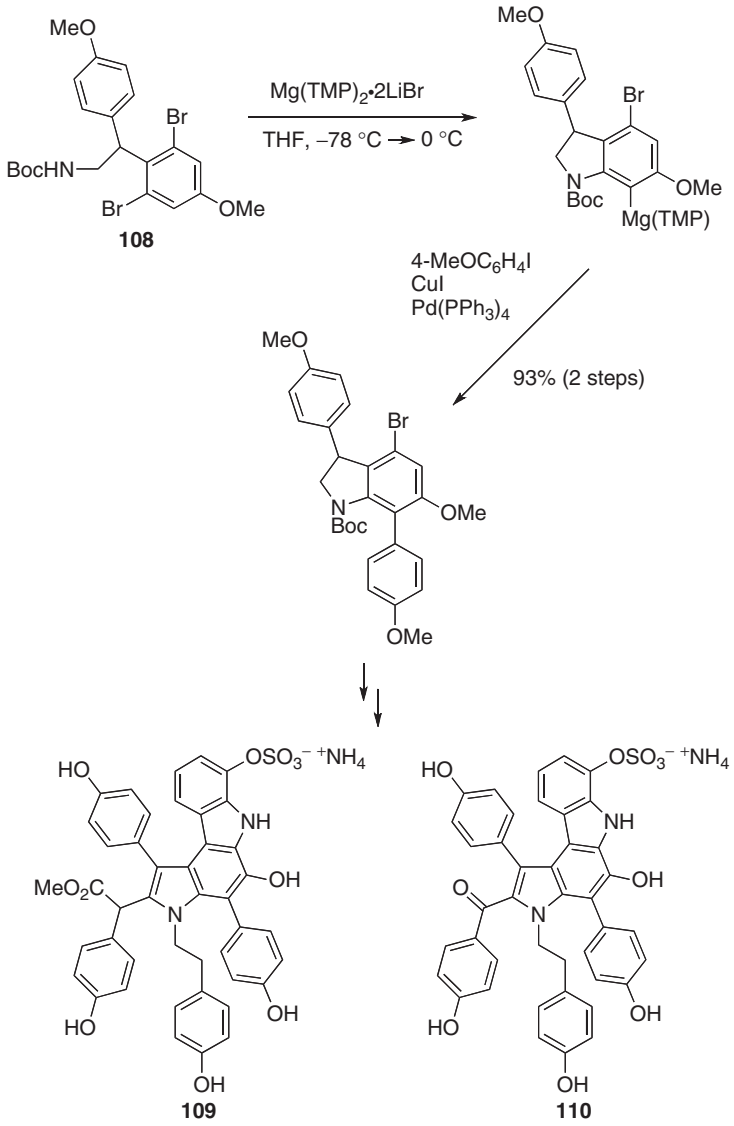
Scheme 91

good yield.[261] In addition, indoline frameworks are fabricated by the reaction of amidine **107** (equation 23)[262] or carbamate **108**, the latter of which has been utilized for total synthesis of dictyodendrin A (**109**) and B (**110**) through cyclization/cross-coupling sequence (**Scheme 92**).[263]



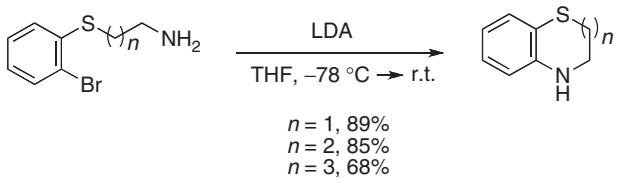
(23)

E = Me, 81% (El = MeI)
E = TMS, 95% (El = TMSCl)
E = Br, 83% (El = $Br(CH_2)_2Br$)

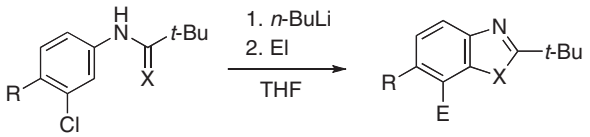


Scheme 92

Installation of a sulfur atom in a tether and variation in chain length allow one-step synthesis of *N*,*S*-heterocycles of varied ring size (equation 24).[264] Oxygen and sulfur nucleophiles likewise take part in the cyclization: benzoxazoles[265] or benzothiazoles[266] are prepared readily from amide **111** or thioamide **112** (equation 25), and furthermore application of the procedure to the synthesis of β_2-adrenoceptor agonist S1319 (**113**) has been reported (**Scheme 93**).[267]



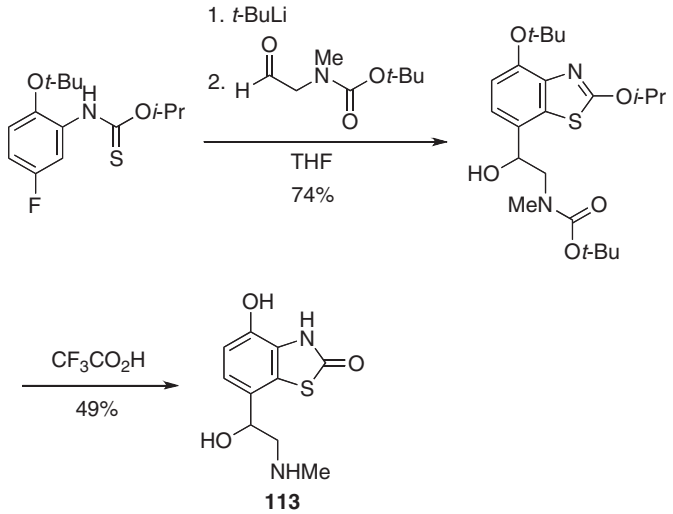
(24)



111 (X = O)
112 (X = S)

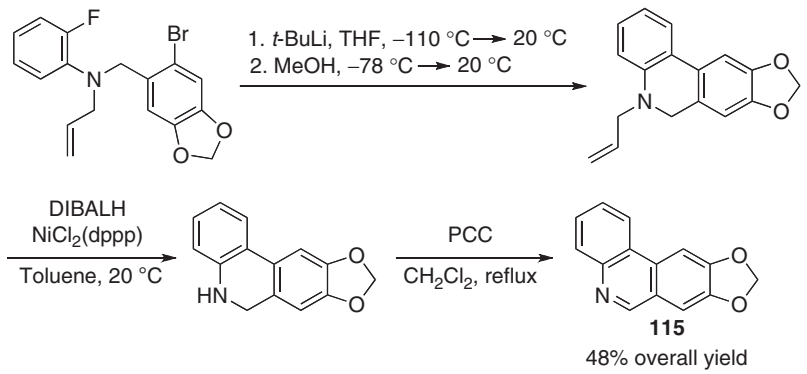
X = O, R = Me, E = CO_2H, 47% (El = CO_2)
X = O, R = MeO, E = CO_2H, 40% (El = CO_2)
X = S, R = H, E = CHO, 63% (El = DMF)
X = S, R = H, E = CONH*t*-Bu, 61% (El = *t*-BuNCO)

(25)

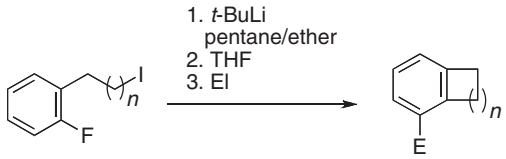


Scheme 93

The cyclization of aryne-tethered alkyllithiums offers direct access to substituted benzocyclobutenes, indans, and tetralins (equation 26),[268,269] and the reaction has been extended to synthesis of indoles by use of *N*-(bromoallyl)aniline **114** (equation 27).[270,271] In addition, a variety of dibenzoheterocyclic structures can be constructed efficiently by intramolecular aryl–aryl bond-forming processes through the aryne cyclization (equation 28),[272,273] and the synthetic utility of this methodology has been demonstrated by total synthesis of trisphaeridine (**115**, Scheme 94) and *N*-methylcrinasiadine (**116**, Scheme 95).[274]

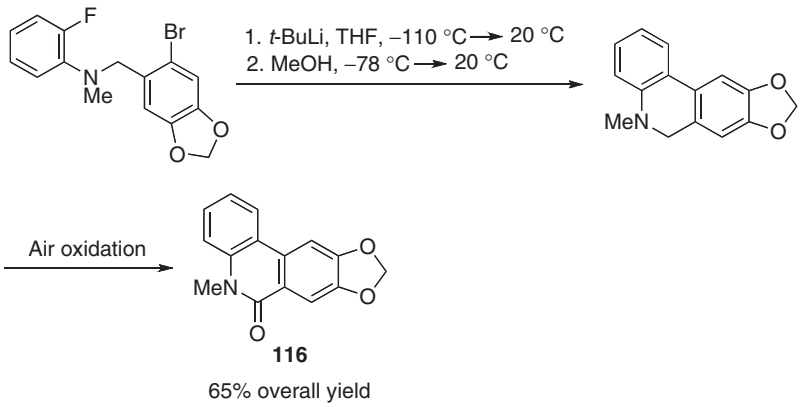


Scheme 94



(26)

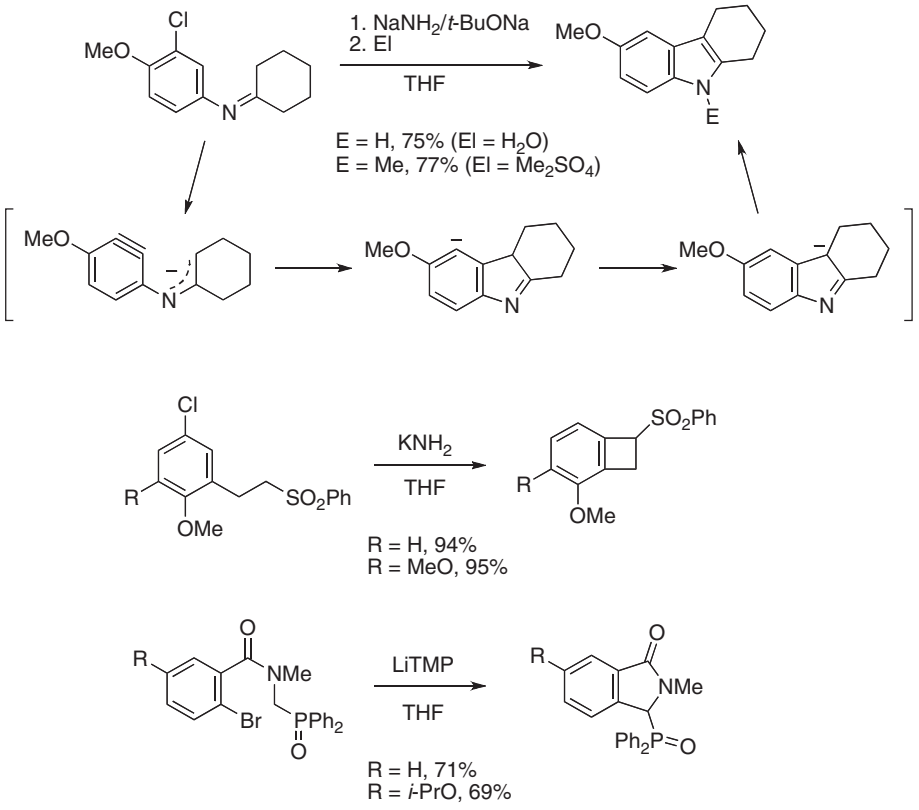
n = 1, E = CHO, 32% (El = DMF)
n = 2, E = Br, 62% (El = $Br(CH_2)_2Br$)
n = 2, E = CO_2Et, 66% (El = $ClCO_2Et$)
n = 3, E = CHO, 35% (El = DMF)



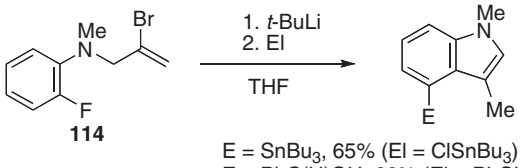
116

65% overall yield

Scheme 95



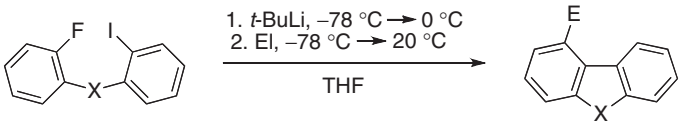
Scheme 96



114

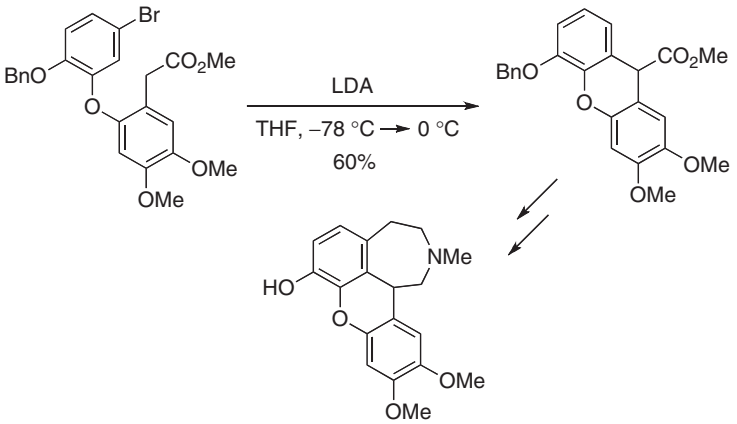
(27)

E = $SnBu_3$, 65% (El = $ClSnBu_3$)
E = PhC(H)OH, 66% (El = PhCHO)
E = CO_2Et, 55% (El = $ClCO_2Et$)

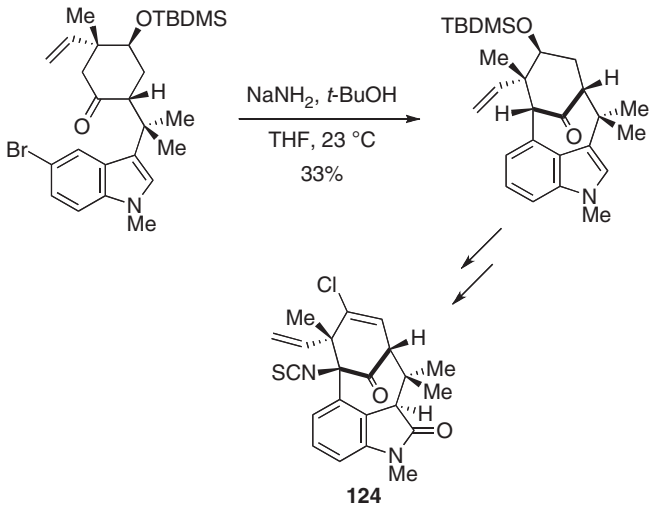


(28)

X = NMe, E = SPh, 64% (El = PhSSPh)
X = NMe, E = Br, 70% (El = $Br(CH_2)_2Br$)
X = O, E = 4-MeC_6H_4CO, 62% (El = 4-MeC_6H_4CN)
X = O, E = CO_2Et, 67% (El = $ClCO_2Et$)
X = S, E = SPh, 78% (El = PhSSPh)
X = S, E = 4-$MeC_6H_4C(H)OH$, 75% (El = 4-MeC_6H_4CHO)



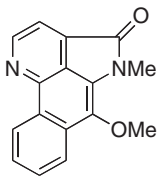
123



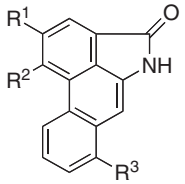
124

Scheme 97

Extensive studies have been conducted on the cyclization using stabilized carbanions containing imine,[275,276] sulfonyl,[277] or phosphinyl moiety,[278,279] that give indole, benzocyclobutene, or isoindolinone derivatives, respectively (Scheme 96). The phosphinyl-substituted isoindolinones act as versatile intermediates in total synthesis of such naturally occurring alkaloids as eupolauramine (**117**),[280] enterocarpam II (**118**),[281] taliscanine (**119**),[281] velutinam (**120**),[281] and cepharanone A (or B) (**121** and **122**).[282] Similarly, the enolate-based cyclization has been employed in synthesis of clavizepine (**123**)[283] and *N*-methylwelwitindolinone C isothiocyanate (**124**) (Scheme 97).[284]

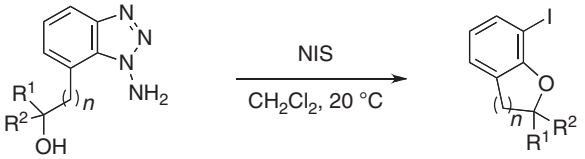


117



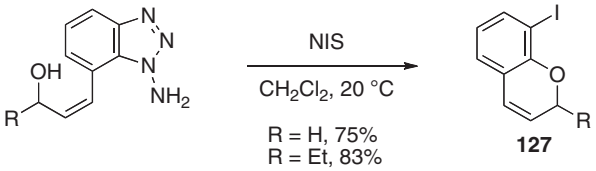
118: $R^1 = R^2 = OMe$, $R^3 = OH$
119: $R^1 = R^2 = R^3 = OMe$
120: $R^1 = OH$, $R_2 = R^3 = OMe$
121: $R^1 + R^2 = CH_2OCH_2$, $R^3 = H$
122: $R^1 = R^2 = OMe$, $R^3 = H$

Aminobenzotriazoles having a hydroxy group in a tether are smoothly transformable into *O*-heterocycles including dihydrobenzofuran (**125**),[98,285] chroman (**126**),[98,286,287] chromene (**127**),[286,287] and xanthene (**128**)[288,289] derivatives under oxidation conditions using NIS (see Section 4.09.2.4), whereas incorporating an iodine atom adjacent to the newly formed C–O bond (Scheme 98). Formal total synthesis of α-tocopherol (**129**) featuring this cyclization has also been accomplished (Scheme 99).[290]



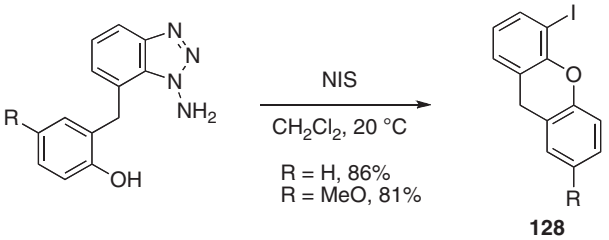
$n = 1$, **125**
$n = 2$, **126**

R^1 = Ph, R^2 = H, n = 1, 86%
R^1 = n-C_5H_{11}, R^2 = H, n = 1, 92%
R^1 = Et, R^2 = H, n = 2, 85%
$R^1 = R^2$ = Me, n = 2, 90%



R = H, 75%
R = Et, 83%

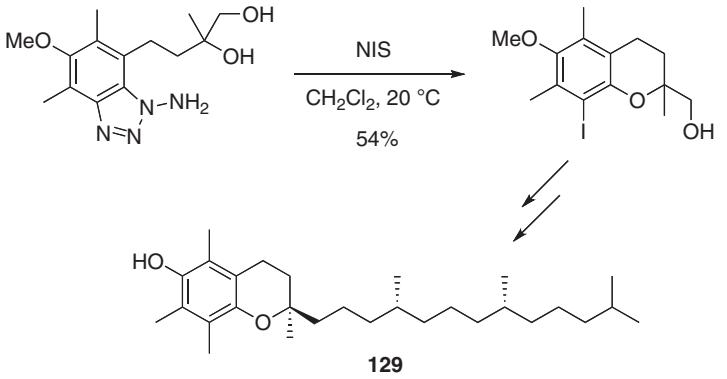
127



R = H, 86%
R = MeO, 81%

128

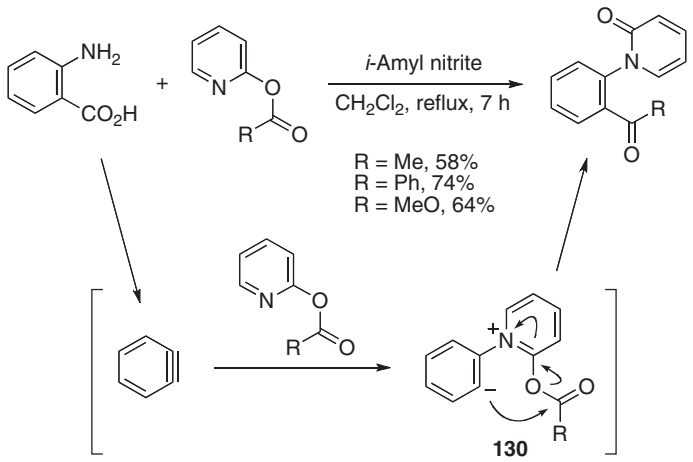
Scheme 98



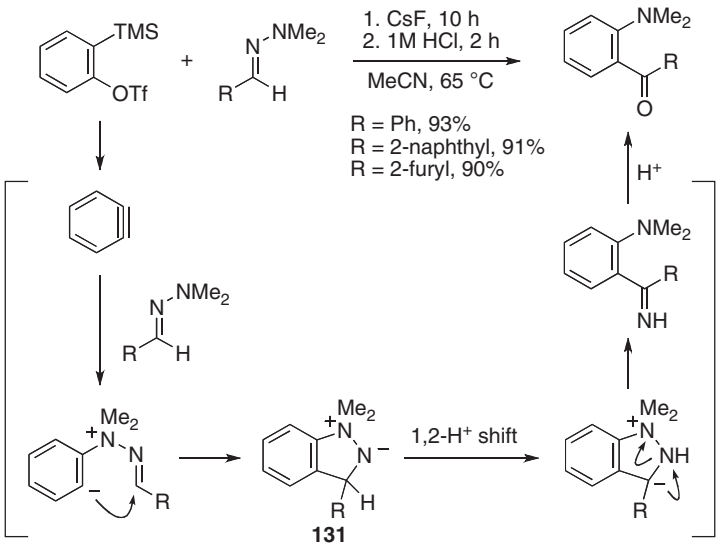
Scheme 99

4.09.3.2.7 Miscellaneous

Reaction of arynes with 2-pyridyl carboxylates affords 1-(2-acylphenyl)-2-pyridones in good yields.[291] Similar to the pathway for the insertion reaction (see Section 4.09.3.2.2), the reaction proceeds through a formation of zwitterion **130** and subsequent intramolecular nucleophilic substitution (Scheme 100).

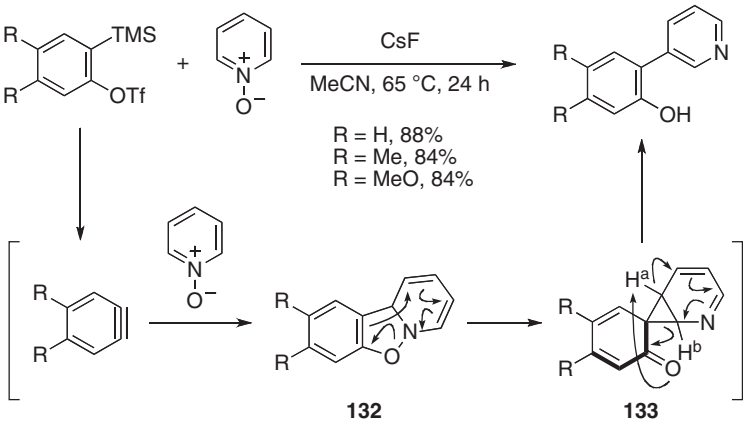


Scheme 100



Scheme 101

Various *ortho*-(dimethylamino)aryl ketones are produced by treating arynes with 1,1-dimethylhydrazones.[292] As shown in Scheme 101, five-membered intermediate **131**, arising from a formal [3 + 2] cycloaddition, undergoes 1,2-H^+ shift and ring-opening to give an imine, which is finally converted into the ketone on hydrolysis. A formal [3 + 2] cycloaddition is also operative in a reaction of arynes with pyridine *N*-oxides which provides 3-(2-hydroxyphenyl)pyridines.[293] The resulting tricyclic compound (**132**) then isomerizes to spiro intermediate **133**, whose carbonyl oxygen abstracts H^a to generate the product (Scheme 102).



Scheme 102

4.09.4 Conclusive Remarks

A variety of nucleophilic couplings with arynes described in this chapter have demonstrated the rich chemistry of arynes and their high synthetic utility for constructing diverse aromatic compounds. A marked resurgence of interest in the nucleophilic couplings, especially in the past decade, would be ascribable to the use of 2-(trimethylsilyl)aryl triflates as aryne precursors, which allows the generation of arynes under extremely mild conditions. In view of an increasing demand for the efficacious and selective synthesis of aromatic compounds found widely in various functional molecules, development of new nucleophilic couplings with arynes still continues to be an important subject in synthetic organic chemistry.

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4.10 Reactions of Nucleophiles with Coordinated Alkynes, Alkenes, and Allenes

W Bai, J Chen, and G Jia, University of Science and Technology, Kowloon, Hong Kong

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4.10.1 Introduction

Alkynes, alkenes, and allenes are widely available starting materials for organic synthesis. These species normally do not react readily with nucleophiles. However, their reactivity toward nucleophile can be enhanced on coordination to a metal center. The enhanced reactivity can be attributed to metal-ligand interaction which results in a net withdrawing of electron density from the unsaturated hydrocarbon ligands to the metal centers.

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Nucleophilic addition on coordinated alkynes, alkenes, and allenes has been intensively studied because of the great importance for the transformation or functionalization of these unsaturated hydrocarbons. The reaction has been recognized as one of the key steps in catalytic cycles of numerous catalytic reactions,[1] for example, Wacker oxidation and related process, hydroamination, hydration, hydroalkoxylation, expoxidation, hydrophosphination, hydroalkylation, hydroarylation, and hydrovinylation. Many stoichiometric nucleophilic addition reactions of coordinated alkynes, alkenes, and allenes are now documented in the literature. There are also many interests in the use of the chemistry in the development of organic/organometallic synthesis with stoichiometric amounts of organometallic reagents.[2] For example, the reaction has been used to make metallacycles that are useful as catalytic precursors or materials.[3]

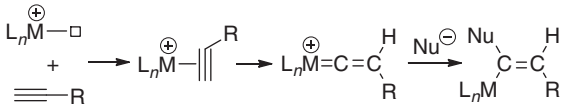
This chapter mainly concerns stoichiometric nucleophilic addition reactions of alkynes, alkenes, and allenes coordinated to mononuclear transition metal centers with carbon-, nitrogen-, oxygen-, and phosphorus-based nucleophiles. Nucleophilic attack of a coordinated unsaturated ligand can proceed by either an outer sphere mechanism in which a nucleophile directly attacks on the coordinated ligand or an inner-sphere mechanism, in which a nucleophile first coordinates to a metal center followed by a 1,2-migratory insertion reaction. Owing to the limitation of the scope of this chapter, reactions involving the second pathway will not be covered. Reactions involving other coordinated unsaturated hydrocarbon ligands (for example, polyenes and polyenyl[4]) will also be excluded.

Excellent reviews on some aspects of the topic have appeared in the literatures, which include the chapter published in 1986 by Bäckvall on nucleophilic attack on coordinated alkenes,[5] the articles published in 1991 by Hegedus on reactions of carbon- and herteroatom nucleophiles with alkenes and alkynes,[2] the chapter published in 1986 by Davidson on reactions of coordinated alkynes,[6] and the chapter published in 1995 by McDaniel on nucleophilic attack on alkene complexes.[7]

4.10.2 Reactions of Alkynes

Coordinated alkynes can react with a variety of nucleophiles. The products of the reactions are dependent on the coordination sphere of the metal fragment or whether the alkyne is a two-electron-donor or a four-electron-donor. In general, nucleophilic addition to two-electron-donor alkyne ligands produces *trans*-η^1-vinyl complexes, and reactions involving four-electron-donor alkyne ligands yield η^2-vinyl (or metallacyclopropene) complexes.[8]

Many late transition metal complexes react with terminal alkynes to give vinylidene complexes.[9] It has also been established that nucleophiles can attack the α-carbons of vinylidene ligands. Therefore, transition metal-mediated nucleophilic addition reactions of terminal alkynes may involve vinylidene intermediates through the sequence shown in Scheme 1, rather than direct attack of nucleophiles on coordinated η^2-alkyne ligands. In fact, there are many reported examples of addition of nucleophiles such as amines,[10] alcohols,[11] and water[12] to vinylidene ligands or terminal alkynes mediated by late transition metals. These reactions, although interesting and important, will not be discussed further, because of the restriction of the scope of this chapter.



Scheme 1

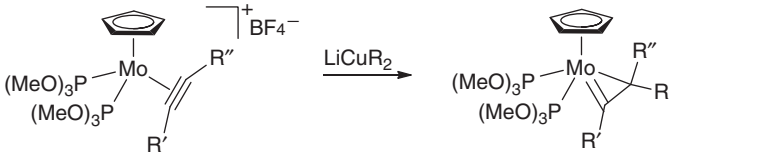
4.10.2.1 Reactions with Hydrides and Carbon-Based Nucleophiles

Nucleophilic addition of hydride and carbon-based nucleophiles to coordinated alkyne ligands has been reported for well-defined alkyne complexes of group 6–8 metals.

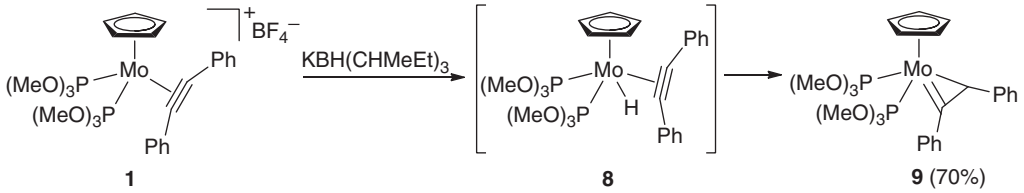
4.10.2.1.1 Reactions of group 6 metal complexes

Reactions of monocationic four-electron-donor alkyne complexes of the type $[CpMo(\eta^2\text{-alkyne})L_2]BF_4$ with cuprates and hydrides have been described by Green and coworkers. They found that these complexes can react with cuprates to give η^2-vinyl complexes. For example, the alkyne complex $[CpMo(PhC{\equiv}CPh)(P(OMe)_3)_2]BF_4$ (**1**) reacted with $LiCuR_2$ (R = Ph, Me) to give the η^2-vinyl complexes $CpMo(\eta^2\text{-}PhCR{=}CPh)(P(OMe)_3)_2$ (**2**, R = Ph; **3**, R = Me) (Scheme 2); the complex $[CpMo(HC{\equiv}CCMe_3)(P(OMe)_3)_2)BF_4$ (**4**) reacted with $LiCuPh_2$ at the terminal alkyne-carbon to give the η^2-vinyl complex **5**; the complex $[CpMo(PhC{\equiv}CMe)(P(OMe)_3)_2]BF_4$ (**6**) reacted with $LiCuPh_2$ at the CPh alkyne-carbon to give the η^2-vinyl complex **7**. It was suggested that the reactions proceed through two competing pathways, namely, direct attack of R^- on the coordinated alkyne-carbon or initial attack of R^- on the metal followed by an insertion of alkyne into the Mo–R bond.[13,14]

Similar η^2-vinyl complexes were produced when complexes of the type $[CpMo(\eta^2\text{-alkyne})L_2]BF_4$ were treated with hydride reagents. For example, the alkyne complex $[CpMo(PhC{\equiv}CPh)(P(OMe)_3)_2]BF_4$ (**1**) reacted with $KHB(CHMeEt)_3$ to give the η^2-vinyl complex **9** (Scheme 3).[13,14] However, the reaction may not proceed by direct attack of hydride on the alkyne-carbon.



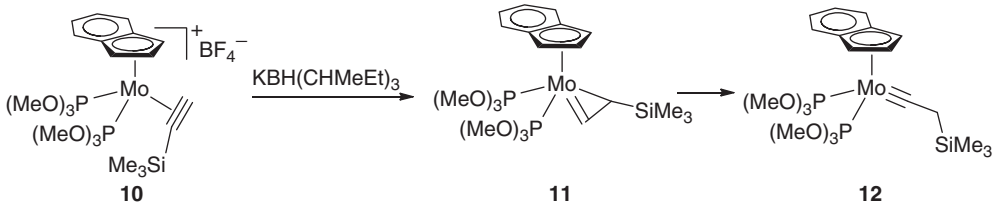
Scheme 2



Scheme 3

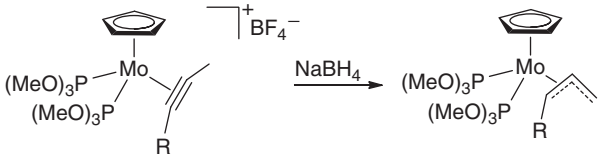
Instead, the η^2-vinyl complex **9** may be formed by initial attack of hydride on the metal to give the hydride intermediate **8** followed by insertion of the alkyne into the Mo–H bond.

The indenyl complex $[(\eta^5\text{-indenyl})Mo(Me_3SiC{\equiv}CH)(P(OMe)_3)_2]BF_4$ (**10**) also reacted with $KHB(CHMeEt)_3$ to afford the η^2-vinyl complex **11** (Scheme 4). The η^2-vinyl complex **11** is unstable and rearranged quantitatively into the alkylidyne complex $(\eta^5\text{-indenyl})Mo{\equiv}CCH_2SiMe_3(P(OMe)_3)_2$ (**12**).[15] A related alkylidyne complex was also isolated from the reaction of $[CpMo(HC{\equiv}CCMe_3)(P(OMe)_3)_2]BF_4$ with sodium borohydride.[16]



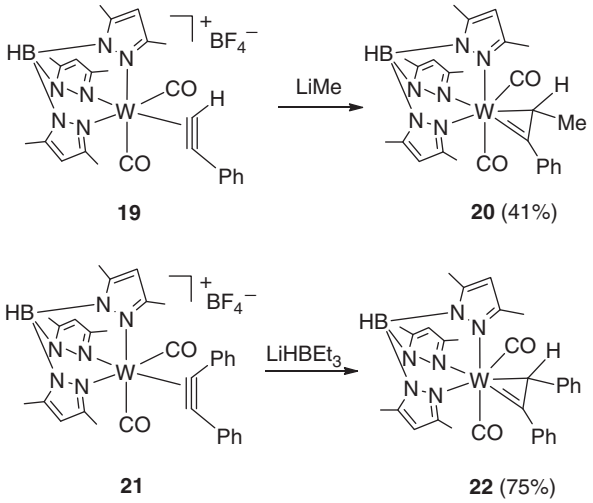
Scheme 4

Reactions of complexes of the type $[CpMo(\eta^2\text{-alkyne})L_2]BF_4$ with hydride reagents could also lead to the formation of other products. For example, the alkyne complexes $[CpMo(MeC{\equiv}CR)(P(OMe)_3)_2]BF_4$ (**13**, R=Me; **14**, R=Et; **15**, R=*i*-Pr) reacted with $NaBH_4$ or $KBH(CHMe_2)_3$ to give the η^3-allyl complexes $CpMo(\eta^3\text{-}CH_2CHCHR)(P(OMe)_3)_2$ (**16**, R=Me; **17**, R=Et; **18**, R=*i*-Pr), presumably through isomerization of the vinyl intermediates $CpMo(CH_3C{=}CHR)(P(OMe)_3)_2$ (Scheme 5).[17] The isomerization proceeds via initial rearrangement of the vinyl intermediates $CpMo(CH_3C{=}CHR)(P(OMe)_3)_2$ to hydrido-allene complexes $CpMoH(CH_2{=}C{=}CHR)(P(OMe)_3)_2$ followed by insertion of the allene into the Mo–H bond. Similarly, η^3-allyl complexes were also obtained from the reactions of $NaBH_4$ or $KBH(CHMe_2)_3$ with complexes such as $[CpMo(MeC{\equiv}CMe)(Ph_2PCH{=}CHPPh_2)]BF_4$, $[(\eta^5\text{-indenyl})Mo(MeC{\equiv}CMe)(P(OMe)_3)_2]BF_4$, and $[CpMo(MeC{\equiv}CMe)(PEt_3)(CO)]BF_4$.



Scheme 5

Reactions of monocationic four-electron-donor alkyne tungsten complexes supported by a Tp′ ligand (Tp′ = hydridotris(3,5-dimethylpyrazolyl)borate) with LiMe and $LiBHEt_3$ have been described by Templeton and coworkers. Treatment of the cationic alkyne complex $[Tp'(CO)_2W(PhC{\equiv}CH)]BF_4$ (**19**) with MeLi produced the η^2-vinyl complex **20**, as a result of selective attack of CH_3^- on the terminal alkyne-carbon (Scheme 6). The reaction of the alkyne complex $[Tp'(CO)_2W(PhC{\equiv}CPh)]BF_4$ (**21**) with $LiHBEt_3$ produced the analogous η^2-vinyl complex **22**.[18,19]

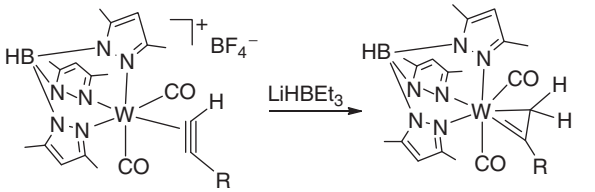


19 **20** (41%)

21 **22** (75%)

Scheme 6

Similarly, the terminal alkyne complexes $[Tp'(CO)_2W(RC{\equiv}CH)]BF_4$ (**23**, R = Me; **24**, R = *n*Bu; **25**, R = CH_2Ph) reacted with $LiHBEt_3$ to produce the η^2-vinyl complexes $[Tp'(CO)_2W(RC{=}CH_2)]$ (**26**, R = Me; **27**, R = *n*Bu; **28**, R = CH_2Ph), as a result of attack of hydride on the terminal alkyne-carbon (Scheme 7).[18–20]



23, R = Me
24, R = *n*-Bu
25, R = CH_2Ph

26, R = Me (81%)
27, R = *n*-Bu (65%)
28, R = CH_2Ph (45%)

Scheme 7

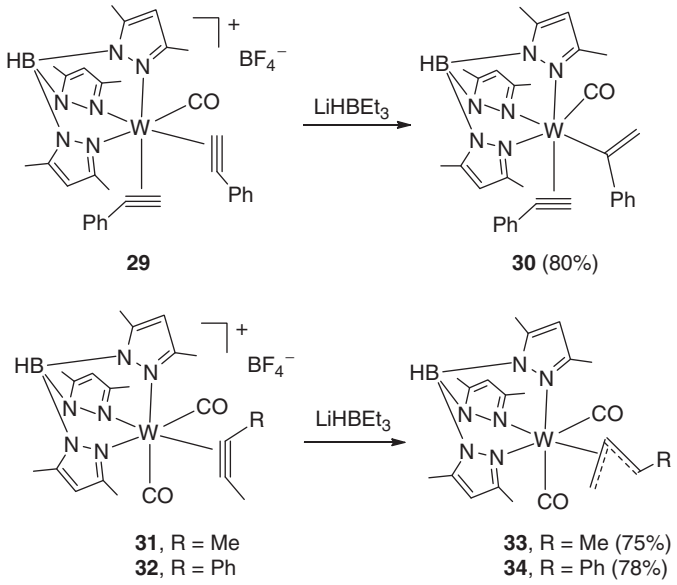
In contrast, the reaction of $LiHBEt_3$ with the bisalkyne complex $[Tp'(CO)_2W(PhC{\equiv}CH)_2]BF_4$ (**29**) produced the η^1-vinyl complex **30** (Scheme 8).[21] Treatment of $[Tp'(CO)_2W(MeC{\equiv}CR)]BF_4$ (**31**, R = Me; **32**, R = Ph) with $LiBHEt_3$ gave the η^3-allyl complexes $Tp'(CO)_2W(CH_2CHCHR)$ (**33**, R = Me; **34**, R = Ph), presumably via η^2-vinyl intermediates $Tp'(CO)_2W(\eta^2\text{-}CH_3C{=}CHR)$,[19] which initially isomerize to the hydrido-allene complexes $Tp'(CO)_2WH(CH_2{=}C{=}CHR)$ and then to the η^3-allyl complexes by insertion of the allene into the W–H bond.

Davidson et al. reported that the alkyne ligand $CF_3C{\equiv}CCF_3$ in complexes of the type $CpMX(CF_3C{\equiv}CCF_3)_2$ (M = Mo, W) can even be attacked by isocyanides to give η^2-vinyl complexes.[22] For example, treatment of $CpMo(CF_3)(CF_3C{\equiv}CCF_3)_2$ (**35**) and $CpWCl(CF_3C{\equiv}CCF_3)_2$ (**37**) with $CNCMe_3$ produced the η^2-vinyl complexes **36** and **38**, respectively (Scheme 9).

On the basis of Wade-Mingo's rule,[23] a nucleophile is expected to attack on the alkyne ligand of the bisalkyne complex **39** preferentially. However, experimentally, the complex **39** reacted with RLi (R = H, Me, Ph) to give complexes **40–42**, as a result of nucleophilic attack of R^- on the η^5-ligand (Scheme 10).[24]

4.10.2.1.2 Reactions of group 7 metal complexes

Limited examples of nucleophilic addition of hydride and carbon-based nucleophiles to alkyne ligands coordinated to group 7 metal centers are known. Treatment of the monocationic alkyne complexes $[CpReBr(PhC{\equiv}CPh)(PPh_3)]BF_4$ (**43**) and [CpReBr

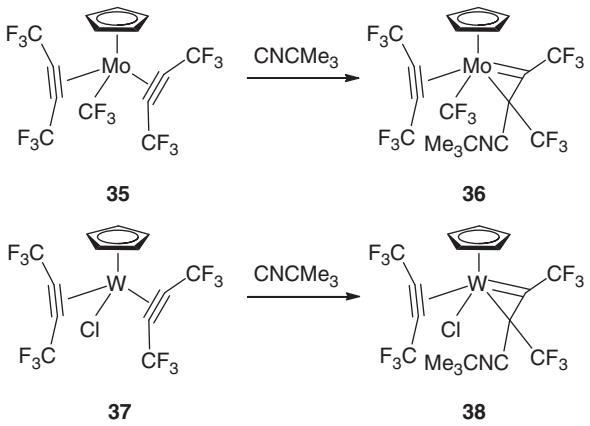


29 **30** (80%)

31, R = Me
32, R = Ph

33, R = Me (75%)
34, R = Ph (78%)

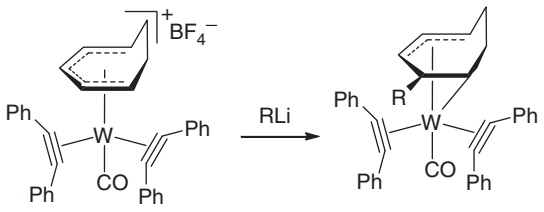
Scheme 8



35 **36**

37 **38**

Scheme 9

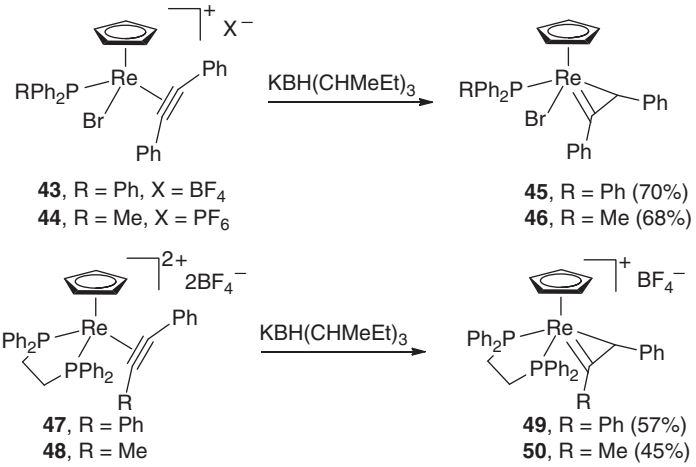


39

40, R = H (90%)
41, R = Me (75%)
42, R = Ph (75%)

Scheme 10

$(PhC{\equiv}CPh)(PMePh_2)_2]PF_6$ (**44**) with $KHB(CHMeEt)_3$ produced the η^2-vinyl complexes **45** and **46**, respectively (Scheme 11). A similar reaction occurred between the dicationic complexes $[CpRe(PhC{\equiv}CR)(dppe)](BF_4)_2$ (**47**, R = Ph; **48** = Me) and $KHB(CHMeEt)_3$ to give the η^2-vinyl complexes $[CpRe(RC{\equiv}CHPh)(dppe)]BF_4$ (**49**, R = Ph; **50**, R = Me).[25]



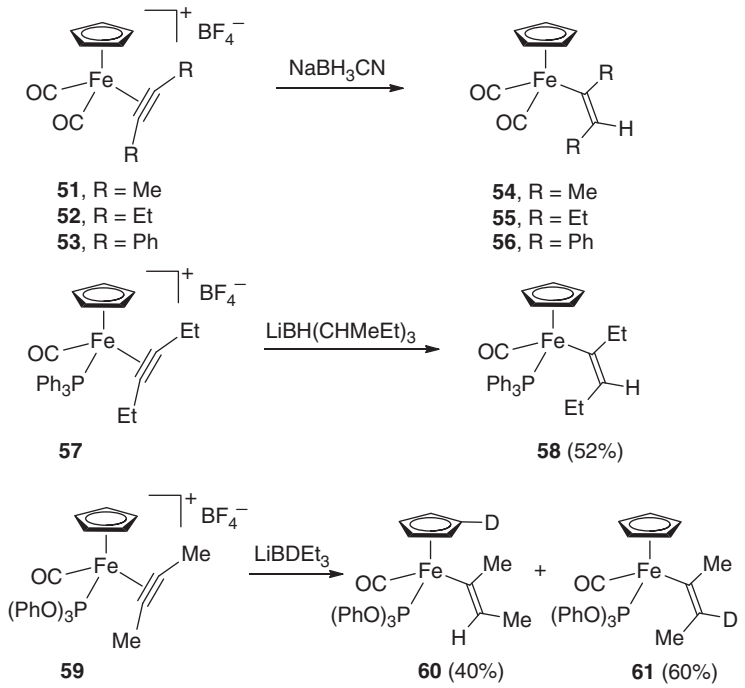
43, R = Ph, X = BF_4
44, R = Me, X = PF_6
45, R = Ph (70%)
46, R = Me (68%)
47, R = Ph
48, R = Me
49, R = Ph (57%)
50, R = Me (45%)

Scheme 11

4.10.2.1.3 Reactions of group 8 metal complexes

A number of examples of nucleophilic addition of hydride and carbon-based nucleophiles to internal alkyne ligands of iron complexes of the type $[CpFe(alkyne)L_2]^+$ have been reported.

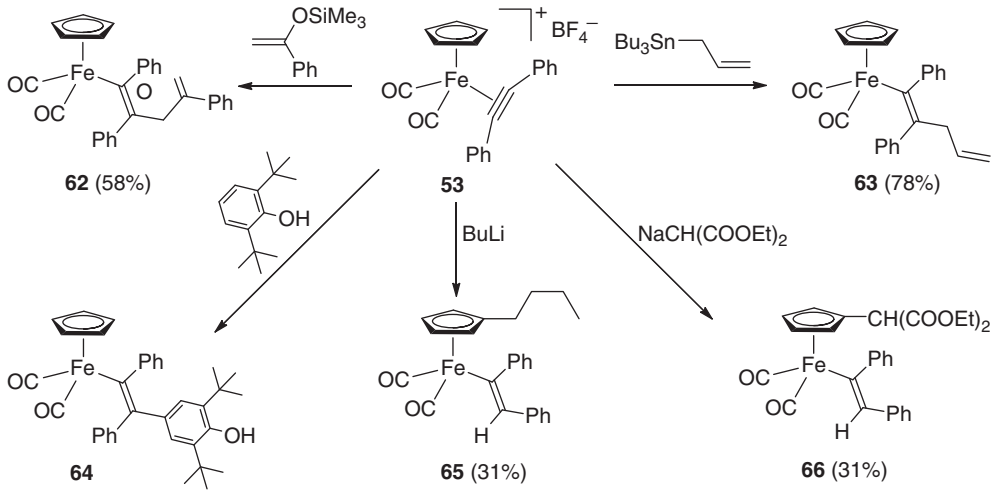
In general, hydride attacks on the alkyne ligands of $[CpFe(alkyne)L_2]^+$ to give *trans*-vinyl complexes. For example, the reactions of $[CpFe(RC{\equiv}CR)(CO)_2]BF_4$ (**51**, R=Me; **52**, R=Et; **53**, R=Ph) with $NaBH_3CN$ produced the *trans*-vinyl complexes $CpFe(RC{=}CHR)(CO)_2$ (**54**, R=Me; **55**, R=Et; **56**, R=Ph) (Scheme 12); reactions of $[CpFe(EtC{\equiv}CEt)(CO)(PPh_3)]BF_4$ (**57**) with $LiBH(CHMe_2)_3$ produced the vinyl complex **58**.[26] Similar reactions have been reported for other $[CpFe(alkyne)(CO)(PPh_3)]BF_4$ complexes.[27] There are cases where the reactions produce *cis*-vinyl complexes. For example, $[CpFe(MeC{\equiv}CMe)(CO)(P(OPh)_3)]BF_4$ (**59**) reacted with $Li[BHEt_3]$ to give the vinyl complex $CpFe(RC{=}CHR)(CO)_2$ as a mixture of *Z* (**60**, 57%) and *E* (**61**, 43%) isomers.[28,29] A deuterium-labeling experiment shows that the *Z* isomer is formed by direct *trans* addition of hydride to the alkyne ligand, whereas the *E* isomer is formed by first addition of hydride to the Cp ring followed by internal *cis* transfer of hydrogen from the ring to the alkyne ligand.



51, R = Me
52, R = Et
53, R = Ph
54, R = Me
55, R = Et
56, R = Ph
57
58 (52%)
59
60 (40%)
61 (60%)

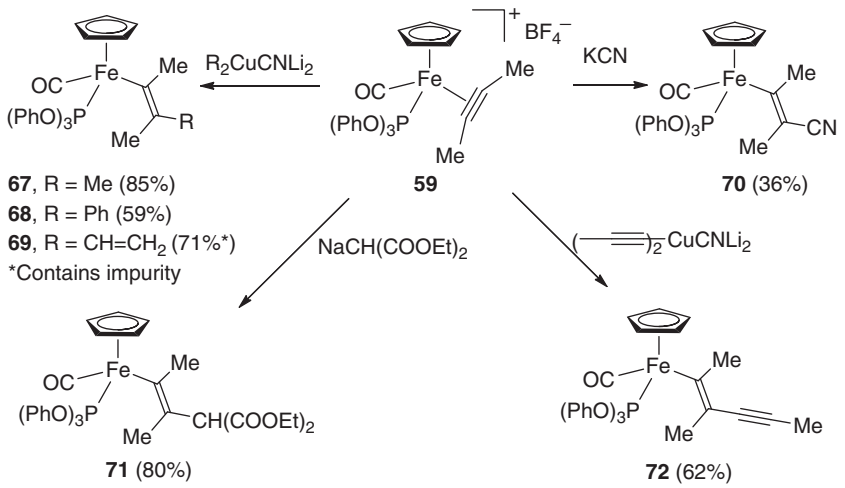
Scheme 12

Several nucleophilic addition reactions of carbon-based nucleophiles have been reported for the alkyne complexes [CpFe(PhC≡CPh)(CO)$_2$]BF$_4$ (**53**) (Scheme 13). The complex reacted with silyl enol ether CH$_2$=CPh(OSiMe$_3$) and allylstannane CH$_2$=CHCH$_2$SnPh$_3$ to give the vinyl complexes **62** and **63**, respectively. It also reacted with NaOC$_6$H$_3$(CMe$_3$)$_2$ at the sterically less congested *p*-position to give the *C*-alkylated product **64**. When *n*-butyllithium and sodium diethyl malonate were used, the reactions gave the substituted cyclopentadienyl complexes **65** and **66**, respectively, because of initial addition of the nucleophiles to the Cp ring followed by internal *cis* transfer of hydrogen from the Cp ring to the alkyne ligand.[30]



Scheme 13

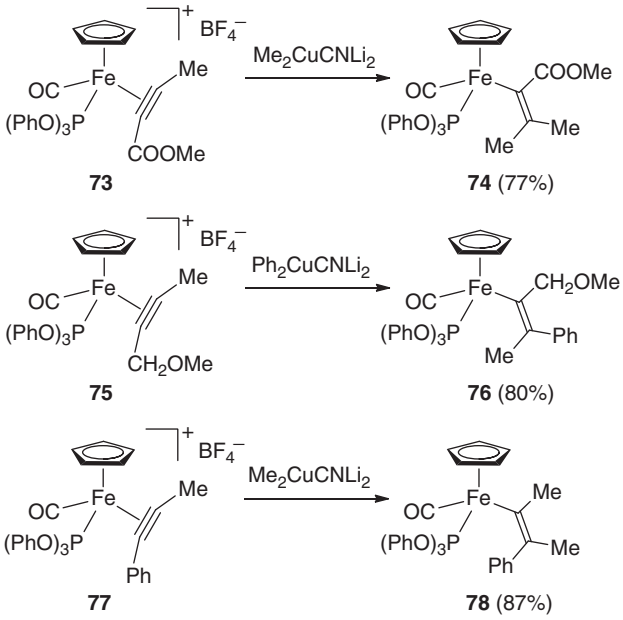
The reactions of [CpFe(alkyne)(CO)(L)]BF$_4$ (L=PPh$_3$, P(OPh)$_3$) with carbon-based nucleophiles have been studied by Reger et al.[31–38] Scheme 14 shows examples of reactions of carbon-based nucleophiles with complexes [CpFe(alkyne)(CO)(L)]BF$_4$ containing a symmetrical alkyne ligand. Scheme 15 shows examples of reactions of carbon-based nucleophiles with complexes [CpFe(alkyne)(CO)(L)]BF$_4$ containing an unsymmetrical alkyne ligand. In general, the reactions produce *trans*-addition vinyl products. Reactions involving unstabilized alkyllithium reagents may also give substituted cyclopentadienyl complexes, because of initial addition of the nucleophiles to the Cp ring followed by internal *cis* transfer of hydrogen from the Cp ring to the alkyne ligands.



Scheme 14

4.10.2.2 Reactions of Nitrogen-Based Nucleophiles

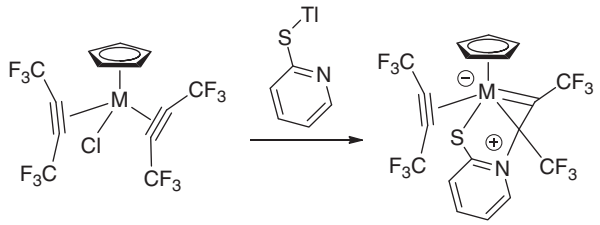
Nucleophilic addition of amines to coordinated alkynes has been suggested as one of the key steps in catalytic hydroamination of alkynes.[39] Stiochiometric addition reactions of nitrogen-based nucleophiles have been demonstrated with well-defined alkyne complexes of metals such as Mo, W, Fe, Co, Ir, Pt, and Au.



Scheme 15

4.10.2.2.1 Reactions of group 6 metal complexes

Nucleophilic addition of pyridine to coordinated $CF_3C{\equiv}CCF_3$ occurred in the reactions of the alkyne complexes $CpMCl(CF_3C{\equiv}CCF_3)_2$ (**37**, M=W; **79**, M=Mo) with thallium pyridine-2-thiolate. The reactions produced the η^2-vinyl complexes **80** and **81** as a result of nucleophilic addition of pyridine to the alkyne ligand (Scheme 16).[40,41] Similarly, η^2-vinyl complexes were obtained when the alkyne complexes **37** and **79** were treated with thallium salts of pyrimidine-2-thiolate and thiazoline-2-thiolate.

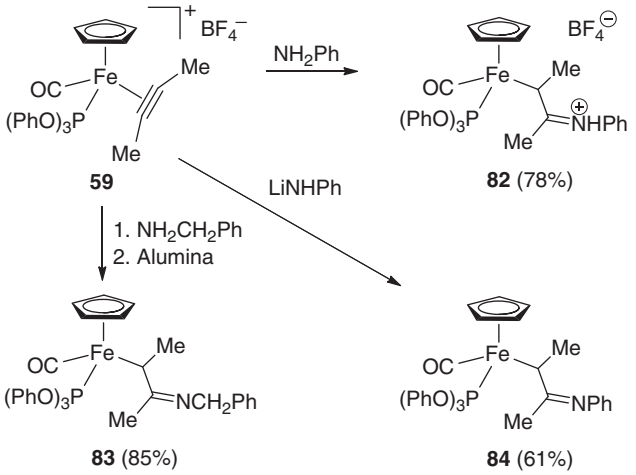


Scheme 16

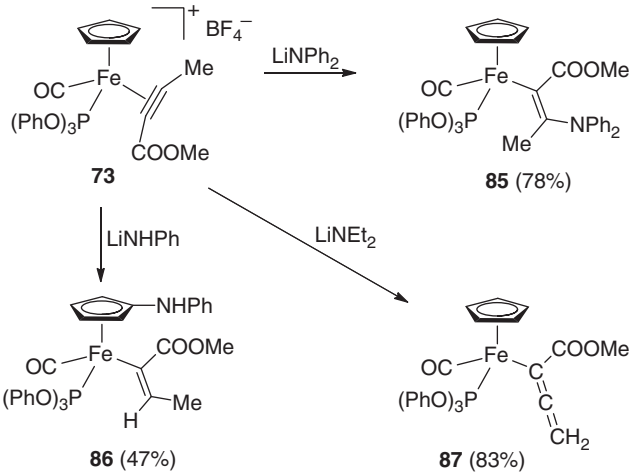
4.10.2.2.2 Reactions of group 8 metal complexes

Reactions of $[CpFe(alkyne)(CO)(L)]BF_4$ (L=phosphine or phosphite) with nitrogen-based nucleophiles have been studied by Reger et al. Scheme 17 shows examples of reactions of nitrogen-based nucleophiles with complexes $[CpFe(alkyne)(CO)(L)]BF_4$ containing a symmetrical alkyne ligand. The iron complex $[CpFe(MeC{\equiv}CMe)(CO)(P(OPh)_3)BF_4$ (**59**) reacted with $PhNH_2$ to give the imine product **82**, presumably through isomerization of the vinyl intermediate $[CpFe\{MeC{=}C(NH_2Ph)Me\}(CO)(P(OPh)_3)]BF_4$. Treatment of the alkyne complex $[CpFe(MeC{\equiv}CMe)(CO)(P(OPh)_3)]BF_4$ (**59**) with the primary amine $PhCH_2NH_2$ followed by alumina gave the alkyl complex **83**. The alkyne complex **59** also reacted with PhNHLi to give the alkyl complex **84**.[33]

Scheme 18 shows examples of reactions of nitrogen-based nucleophiles with complexes $[CpFe(alkyne)(CO)(L)]BF_4$ containing an unsymmetrical alkyne ligand.[33] The alkyne complex $[CpFe(MeC{\equiv}CCOOMe)(CO)(P(OPh)_3)]BF_4$ (**73**) reacted with Ph_2NLi (or Ph_2NH followed by treatment with LDA) at the CMe alkyne-carbon to give the *trans*-addition product **85** (Scheme 18). When PhNHLi was allowed to react with the alkyne complex **73**, the reaction produced the vinyl complex **86** as a result of initial addition of the amide to the cyclopentadienyl ring to give $(\eta^4\text{-}C_5H_4\text{-}NHPh)Fe(MeC{\equiv}CCOOMe)(CO)(P(OPh)_3)$ followed by hydrogen shift from the $\eta^4\text{-}C_5H_4$–NHPh ligand to the alkyne ligand. The reaction of the alkyne complex **73** with Et_2NLi yielded the allenyl product **87** as a result of simple deprotonation of the alkyne ligand. It is not clearly defined why $LiNPh_2$, LiNHPh, and $LiNEt_2$ show different reactivities.



Scheme 17



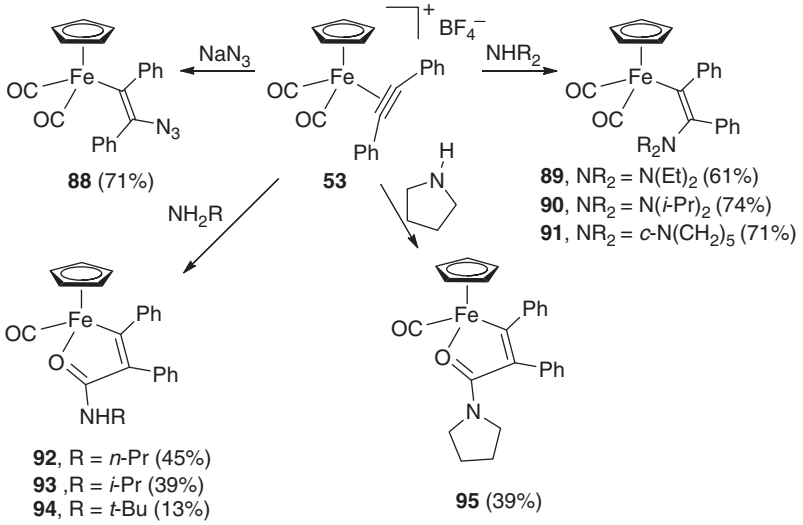
Scheme 18

The reactivity of the iron complexes $[CpFe(RC{\equiv}CR)(CO)_2]BF_4$ (R = Ph, Et) toward nitrogen nucleophilies has been investigated by Akita et al.[30] The reaction of $[CpFe(PhC{\equiv}CPh)(CO)_2]BF_4$ (**53**) with NaN_3 produced the expected *trans*-addition product **88**. Reactions of $[CpFe(PhC{\equiv}CPh)(CO)_2]BF_4$ (**53**) with amines produced two types of products, namely, *cis*-alkenyl complexes or metallacycles, depending on the amines. In general, primary amines tend to produce metallacycles, whereas secondary amines give *cis*-alkenyl complexes as shown in Scheme 19. The reaction with the cyclic secondary amine pyrrolidine also produced the metallacycle **95**. The products were thought to be derived from acyl intermediates formed by initial attack of amines on the CO ligands, followed by intramolecular NR_2/NHR group transfer to the alkyne ligands to give *cis*-alkenyl complexes or insertion of the alkynes into the Fe–acyl bonds to give metallacycles. The expected alkenyl complexes were not formed in the reactions of $[CpFe(CO)_2(EtC{\equiv}CEt)]BF_4$ with amines such as *i*-$PrNH_2$, $(i\text{-}Pr)_2NH$, and piperidine.

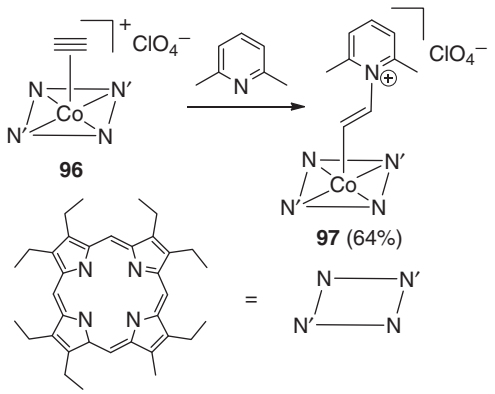
4.10.2.2.3 Reactions of group 9 metal complexes

The alkyne ligand in the cobalt alkyne complex **96** can be attacked by amines.[42–44] For example, the alkyne complex **96** reacted with 2,6-lutidine to give the vinyl complex **97** (Scheme 20). The reaction has been used to prepare vinylene-*Co*,*N*′-linked bis(porphyrin)s and vinylene-*N*,*N*′-linked bis(porphyrin)s.

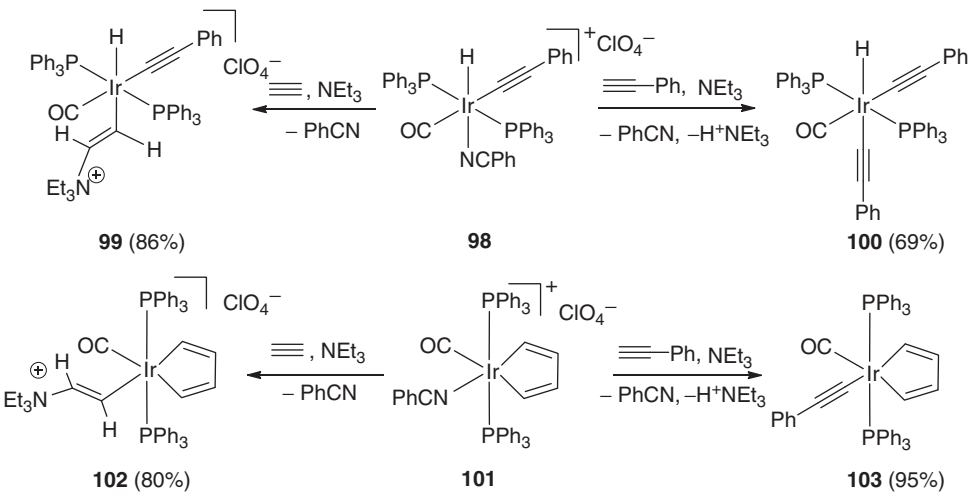
Addition of amines to $HC{\equiv}CH$ coordinated to iridium was observed in the reactions of the iridium complexes **99** and **101** with acetylene/amines. The iridium complexes **98** and **101** reacted with acetylene in the presence of NEt_3 to give the alkenyl products **99** and **102**, respectively (Scheme 21). In the presence of other amines such as NMe_3 and $N(n\text{-}Pr)_3$, the reactions of **98** and **101** with $HC{\equiv}CH$ also gave similar products. In contrast, the reactions of **98** and **101** with phenylacetylene/NEt_3 produce the phenylethynyl ($IrC{\equiv}CPh$) complexes **100** and **103**, respectively.[45]



Scheme 19



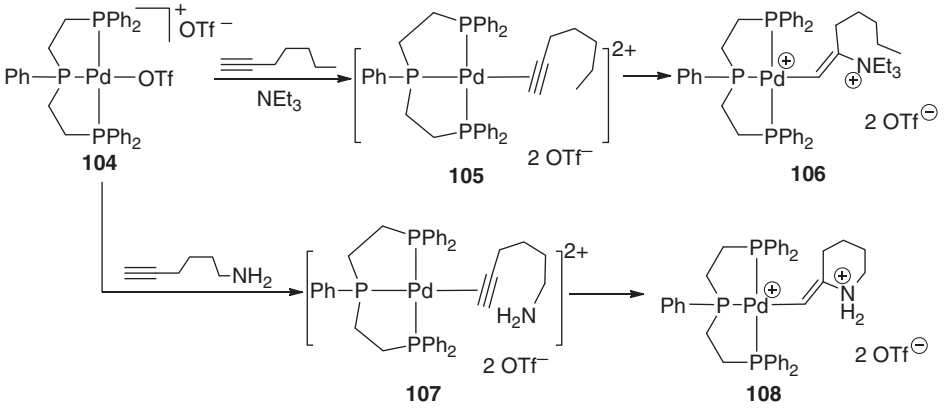
Scheme 20



Scheme 21

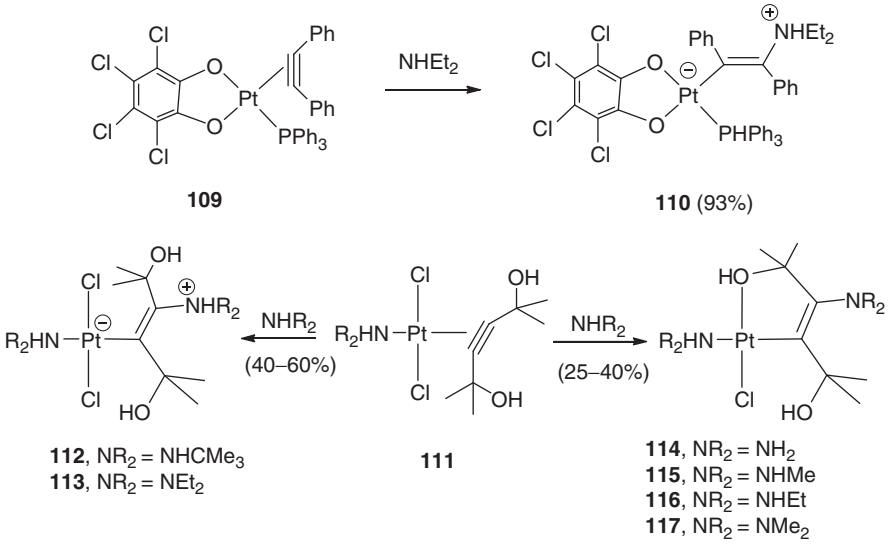
4.10.2.2.4 Reactions of group 10 metal complexes

Addition of amines to alkynes coordinated to palladium was observed in the reactions of the palladium complex [Pd(OTf)(triphos)](OTf) (**104**) (triphos = $PhP(CH_2CH_2PPh_2)_2$) with acetylene/amines (Scheme 22). The complex **104** reacted with heptyne in the presence of NEt_3 to give the vinyl complex **106** through nucleophilic addition of NEt_3 to the intermediate **105**. The complex **104** also reacted with 6-aminohex-1-yne via the intermediate **107** to give the 2-ammonioalken-1-yl complex **108**, which was also detected as the predominant palladium species in the cyclization of 6-aminohex-1-yne to give 2-methyl-1,2-dehydropiperidine catalyzed by the complex [Pd(OTf)(triphos)]OTf (**104**).[46,47]



Scheme 22

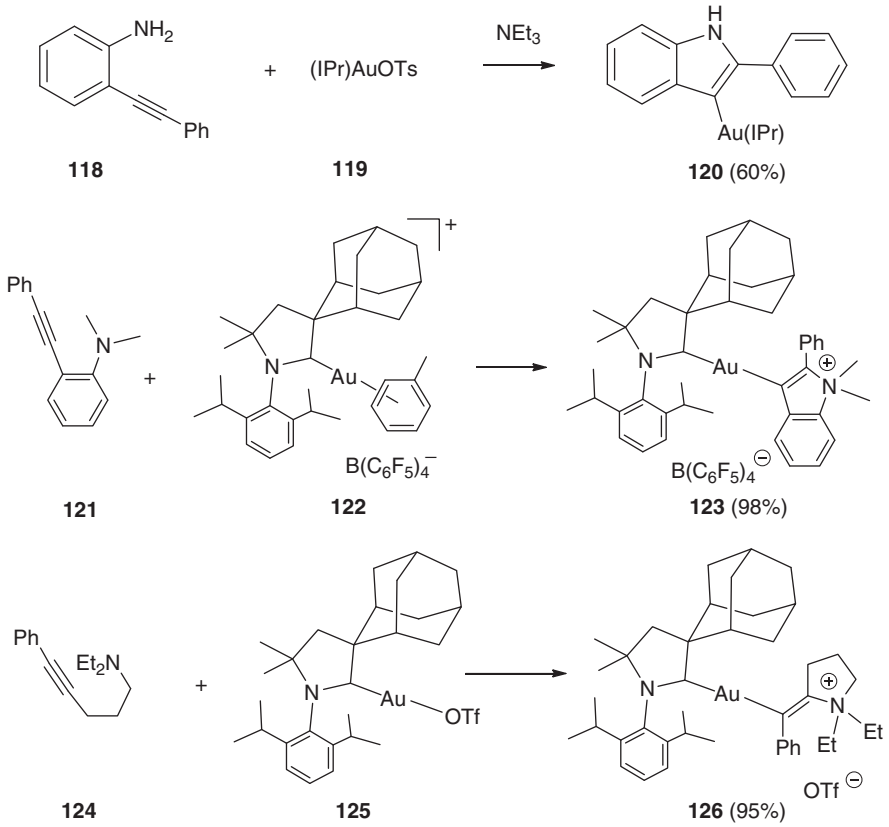
Nucleophilic addition of amines to well-defined platinum alkyne complexes to give *trans*-alkenyl complexes are also known. For example, the platinum complex **109** reacted with $NHEt_2$ to give the vinyl complex **110** (Scheme 23);[48] the complex **111** reacted with amines to produce two kinds of complexes, namely, vinylammonium complexes (e.g., **112–113**), and vinyl amine complexes (e.g., **114–117**), depending on the amines.[49]



Scheme 23

4.10.2.2.5 Reactions of group 11 metal complexes

Nucleophilic attack of nitrogen-based nucleophiles on alkynes coordinated to gold was reported recently. The gold(I) complex (IPr)AuOTs (**119**, IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imida-zol-2-ylidene) reacted with (phenylethynyl)aniline (**118**) and triethylamine to give the organogold compound **120** (Scheme 24).[50] Similarly, the carbene complexes **122** and **125** reacted respectively with the aminoalkynes **121** and **124** to afford the corresponding alkenyl complexes.[51]



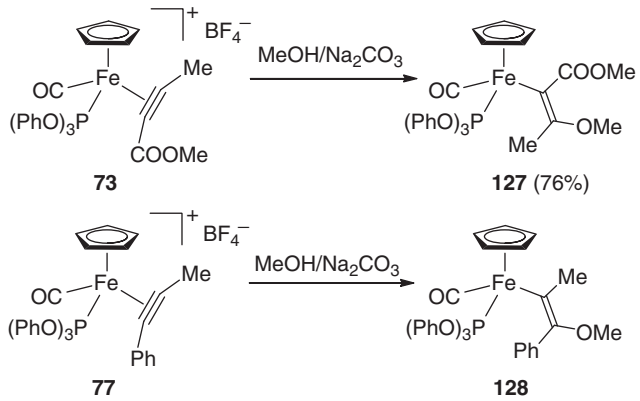
Scheme 24

4.10.2.3 Reactions with Oxygen-Based Nucleophiles

Nucleophilic addition of oxygen-based nucleophiles such as alkoxy and OH to coordinated alkynes is suggested as one of the key steps in catalytic hydroalkoxlation[52] and hydration[53] of alkynes. Stiochiometric addition reactions of oxygen-based nucleophiles have been demonstrated with well-defined alkyne complexes of metals such as Fe, Ru, Ir, Pt, and Au.

4.10.2.3.1 Reactions of group 8 metal complexes

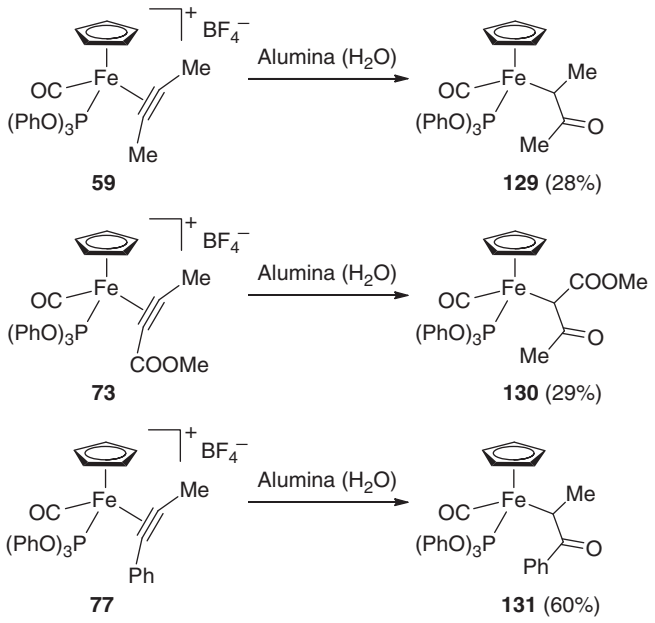
The alkyne ligands of $[CpFe(alkyne)(CO)(P(OPh)_3)]BF_4$ are reactive toward alkoxides. For example, the alkyne complexes $[CpFe(MeC{\equiv}CCO_2Et)(CO)(P(OPh)_3)]BF_4$ (**73**) and $[CpFe(MeC{\equiv}CPh)(CO)(P(OPh)_3)]BF_4$ (**77**) reacted regioselectively with methanol in the presence of Na_2CO_3 to give the vinyl complexes **127** and **128**, respectively (Scheme 25).[33]



Scheme 25

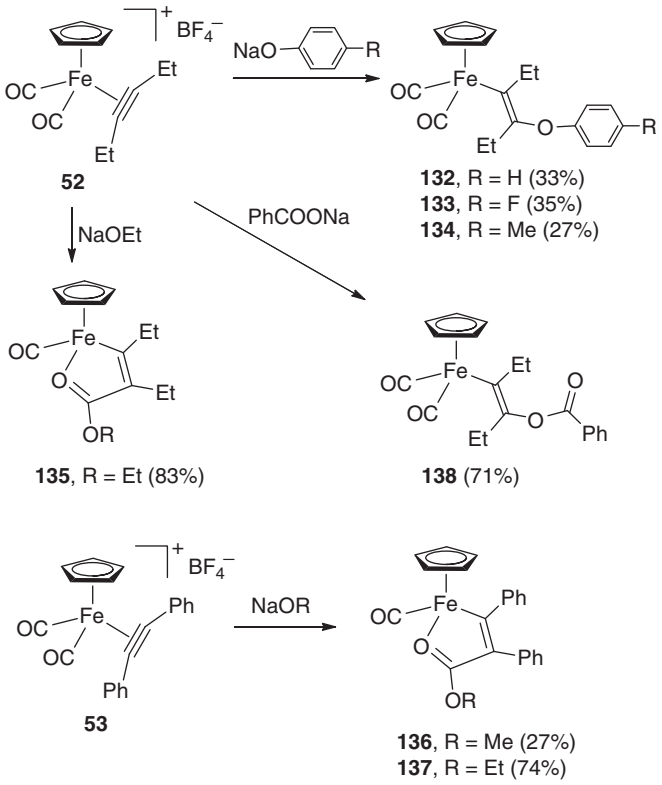
The alkyne ligand of $[CpFe(alkyne)(CO)(P(OPh)_3)]BF_4$ can even be attacked by water. For example, the alkyne complexes $[CpFe(MeC{\equiv}CCMe)(CO)(P(OPh)_3)]BF_4$ (**59**), $[CpFe(MeC{\equiv}CCOOEt)(CO)(P(OPh)_3)]BF_4$ (**73**), and $[CpFe(MeC{\equiv}CCPh)$

$(CO)(P(OPh)_3)]BF_4$ (**77**) were converted into the β-ketonyl complexes **129**, **130**, and **131**, respectively on treatment with alumina (Scheme 26).[33]



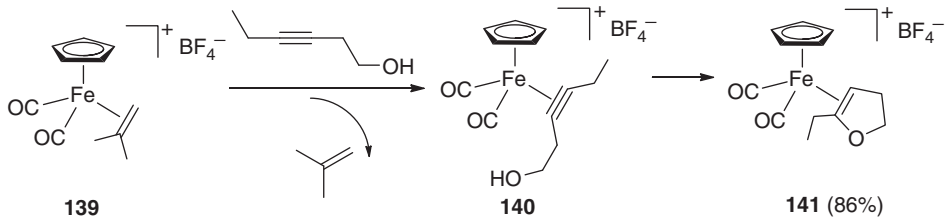
Scheme 26

As expected, complexes $[CpFe(alkyne)(CO)_2]BF_4$ are also reactive toward oxygen-based nucleophiles. As illustrated in Scheme 27 by the reactions of $[CpFe(EtC{\equiv}CEt)(CO)_2]BF_4$ (**52**) and $[CpFe(PhC{\equiv}CPh)(CO)_2]BF_4$ (**53**), the reactions can lead to the formation of *trans*-alkenyl complexes or metallacycles, depending on the structures of the nucleophiles.[30]



Scheme 27

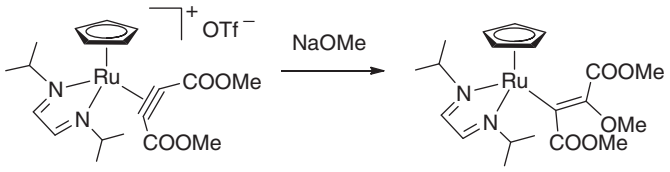
As an additional example of nucleophilic attack of oxygen-based nucleophile on alkyne coordinated to iron, the alkene complex $[CpFe(CH_2{=}CMe_2)(CO)_2]BF_4$ (**139**) reacted with 3-hexyn-1-ol to give the dihydrofuran complex **141** via initial nucleophilic attack of the OH group on the coordinated alkyne-carbon of the intermediate **140** and subsequent protonation (Scheme 28).[54]



139 **140** **141** (86%)

Scheme 28

Examples of nucleophilic addition of oxygen-based nucleophiles to alkynes coordinated to ruthenium are limited. As a rare example, the ruthenium complex **142** reacted with NaOMe to produce the alkenyl complex **143** (Scheme 29).[55]

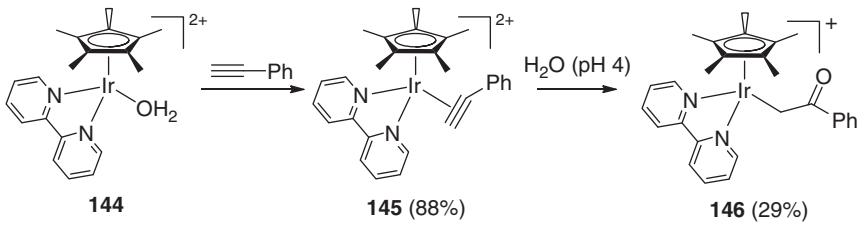


142 **143**

Scheme 29

4.10.2.3.2 Reactions of group 9 metal complexes

Addition of water to alkynes coordinated to iridium was observed in the reaction of the iridium complex $[Cp^*Ir(bipy)(H_2O)]^{2+}$ (**144**) with alkynes in aqueous solution. The complex reacted with phenylacetylene at pH = 4 to give the *β*-ketonyl complex **146**, which is formed by initial nucleophilic attack of water on the alkyne ligand of the intermediate **145** (Scheme 30).[56]



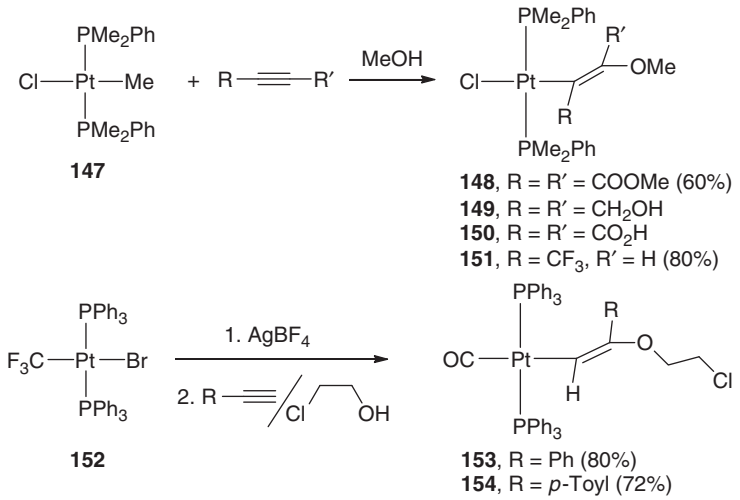
144 **145** (88%) **146** (29%)

Scheme 30

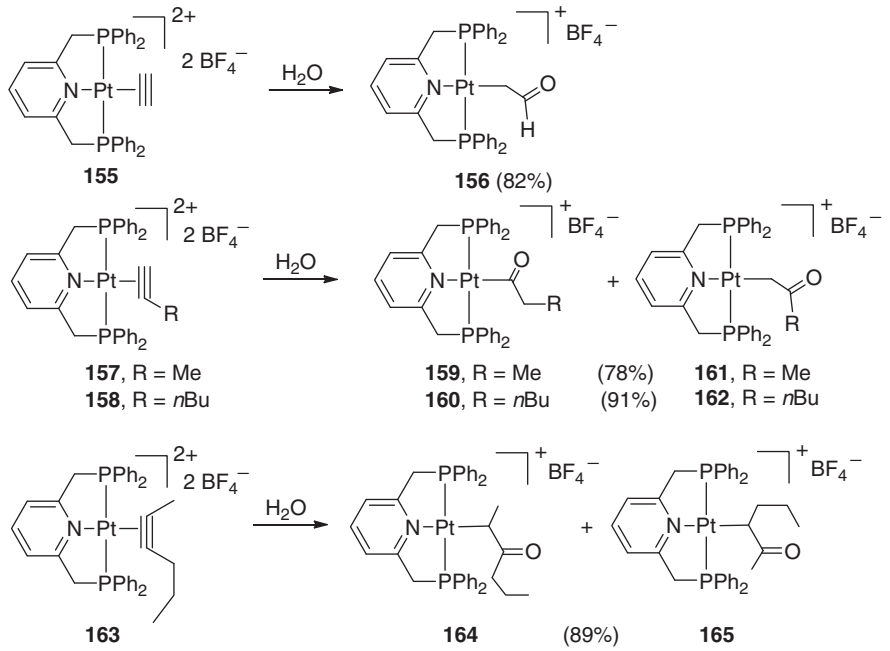
4.10.2.3.3 Reactions of group 10 metal complexes

Several examples of nucleophilic addition of alkoxides to alkynes coordinated to platinum have been reported. For example, the methyl complex $Pt(Me)Cl(PPh_3)_2$ (**147**) reacted with a series of alkynes in methanol to give *trans*-Pt–alkenyl complexes (e.g., complexes **148**–**151**) with the elimination of CH_4 (Scheme 31).[57] The *β*-methoxyvinylplatinum compound **148** was also generated when **147** was treated with HCl/MeOOCC≡CCOOMe in methanolic solution.[58] The complex $Pt(CF_3)Cl(PPh_3)_2$ (**152**) reacted similarly with $AgBF_4$, 1-alkynes RC≡CH (R = Ph, *p*-tolyl) and 2-chloroethanol to produce the *β*-alkoxyalkenyl complexes **153** and **154**.[59] In these reactions, the CO ligand is generated by hydrolysis of the CF_3 group.

Alkynes coordinated to platinum can also be attacked by water. For example, the dicationic acetylene platinum complex **155** reacted with water to form the platina–acetaldehyde complex $[Pt(PNP)(CH_2CHO)]BF_4$ (**156**) (Scheme 32). Analogous complexes with terminal alkynes (e.g., **157**, alkyne = propyne; **158**, alkyne = 1-hexyne) reacted similarly with water to give a mixture of



Scheme 31



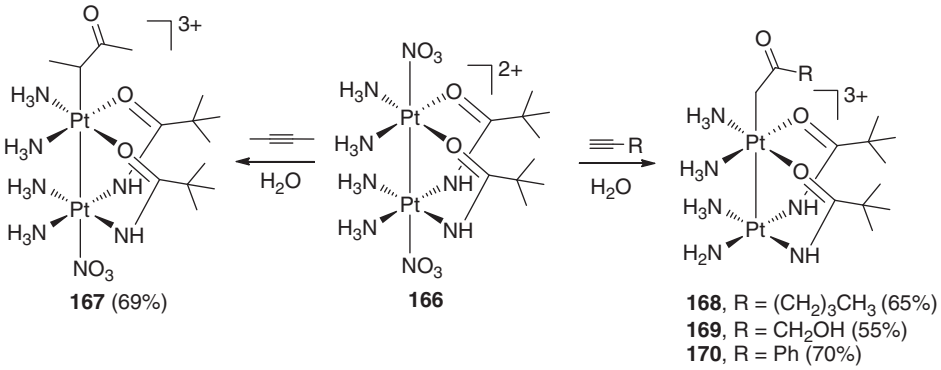
Scheme 32

Markovnikov and *anti*-Markovnikov addition products. Similar complexes with internal alkynes (e.g., **163**) also react with water to form the corresponding *β*-ketonyl complexes.[60] A related *β*-ketonyl complex was formed in the reactions of $[Pt(H_2O)_2((o\text{-}C_6H_4OMe)_2PN(Me)P(o\text{-}C_6H_4OMe)_2)](OTf)_2$ with PhC≡CH and water.[61] It has also been reported that the reaction of *trans*-$PtMe(C{\equiv}CPh)(PPh_3)_2$ with HBF_4 and water produced the hydrolyzed product *trans*-$[PtMe(CO)(PPh_3)_2]BF_4$ and CH_3Ph.[62]

As additional examples of nucleophilic attack of water on alkynes coordinated to platinum, the platinum(III) dimeric complex **166** reacted with both terminal alkynes and internal alkynes in water to give the corresponding ketonyl-Pt(III) dinuclear complexes (e.g., **167**–**170**) (Scheme 33).[63]

4.10.2.3.4 Reactions of group 11 metal complexes

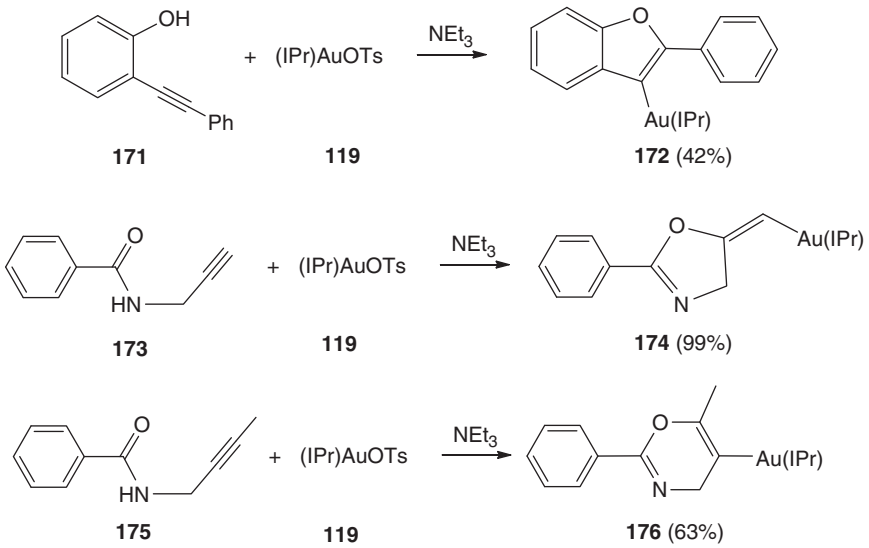
Nucleophilic attack of oxygen-based nucleophiles on alkynes coordinated to gold has been recently reported. The Au(I) complex (IPr)AuOTs (**119**, IPr=*N*,*N*′-bis(2,6-diisopropylphenyl)imida-zol-2-ylidene) reacted with 2-(1-phenylethynyl)phenol (**171**) and triethylamine to give the vinylgold compound **172** (Scheme 34).[50] The complex (IPr)AuOTs (**119**) also reacted with the terminal *N*-propargyl carboxamide **173** in the presence of NEt_3 to produce the five-membered vinylgold complex **174** and with the internal *N*-propargyl carboxamide **175** under similar condition to yield the six-membered vinylgold complex **176**.[64]



167 (69%) **166**

168, R = $(CH_2)_3CH_3$ (65%)
169, R = CH_2OH (55%)
170, R = Ph (70%)

Scheme 33



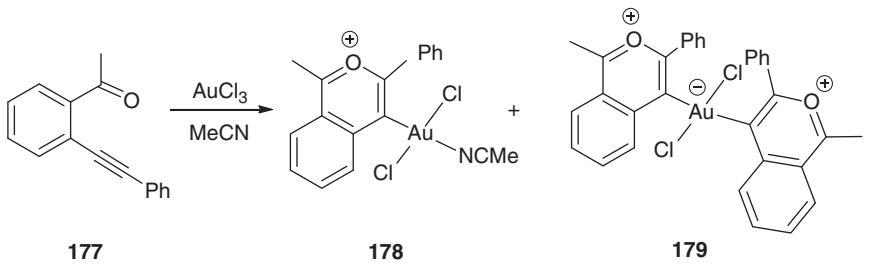
171 **119** **172** (42%)

173 **119** **174** (99%)

175 **119** **176** (63%)

Scheme 34

As an additional example of nucleophilic attack of oxygen-based nucleophiles on alkynes coordinated to gold, the Au(III) vinyl complexes **178** and **179** has been identified (by extended X-ray absorption fine structure (XAFS) analysis MS and NMR) as the major gold species formed in the reaction of 2-carbonylphenylalkyne **177** with $AuCl_3$ in MeCN (Scheme 35).[65]



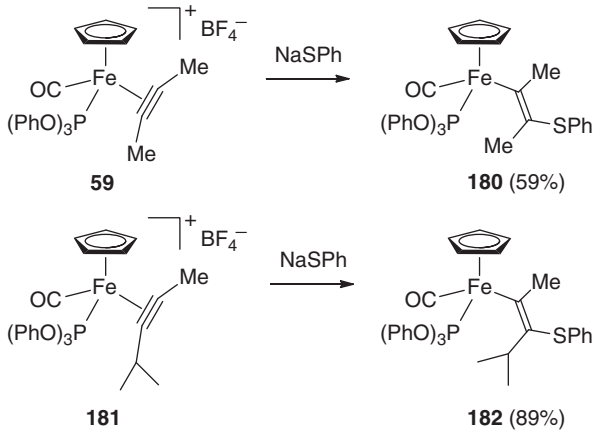
177 **178** **179**

Scheme 35

4.10.2.4 Reactions with Sulfur-Based Nucleophiles

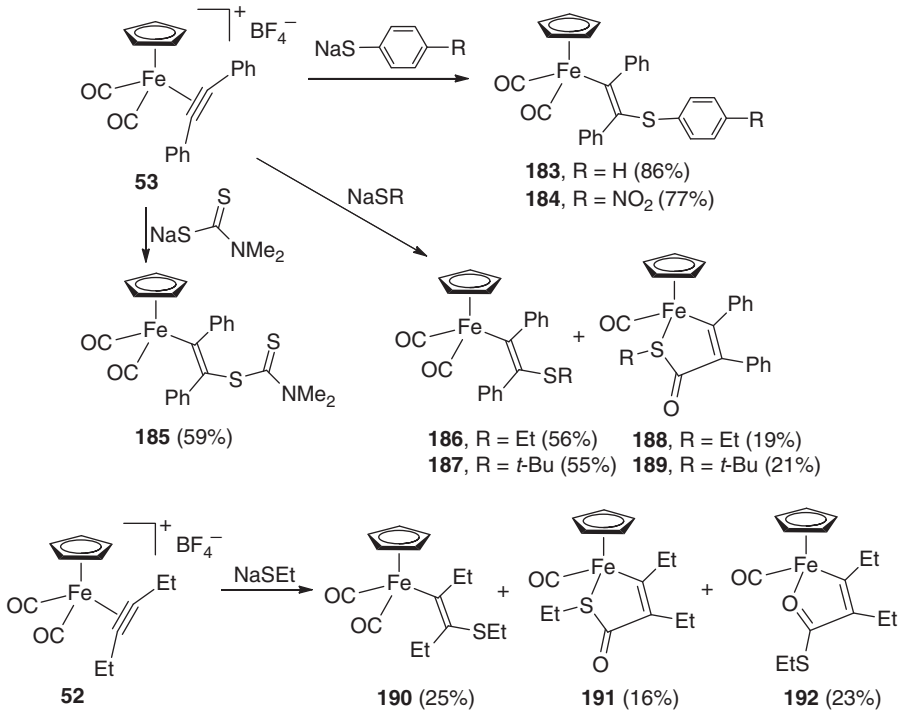
A few examples of nucleophilic addition of sulfur-based nucleophiles to coordinated alkynes have been reported for iron and palladium alkyne complexes.

Reger et al. reported that the iron complexes [CpFe(MeC≡CMe)(CO)($P(OPh)_3$)]BF_4 (**59**) and [CpFe(MeC≡$CCHMe_2$)(CO)($P(OPh)_3$)]BF_4 **181** reacted with NaSPh to give the *trans*-alkenyl complexes **180** and **182**, respectively (Scheme 36).[32,35]



Scheme 36

Akita et al. found that[30] the iron complex [CpFe(PhC≡CPh)(CO)$_2$]BF$_4$ (**53**) reacted with alkanethiolates to yield a mixture of species including the expected *trans*-alkenyl complexes (e.g.**186–187**) and metallacycles (e.g., **188–189**), and with arenethiolates and Na[CS$_2$NMe$_2$] to produce exclusively alkenyl complexes (e.g., **183–185**) (Scheme 37). Under similar condition, [CpFe(EtC≡CEt)(CO)$_2$]BF$_4$ (**52**) reacted with NaSEt to yield a mixture of species, including the *trans*-alkenyl complex **190** and the metallacyclic complexes **191** and **192**.

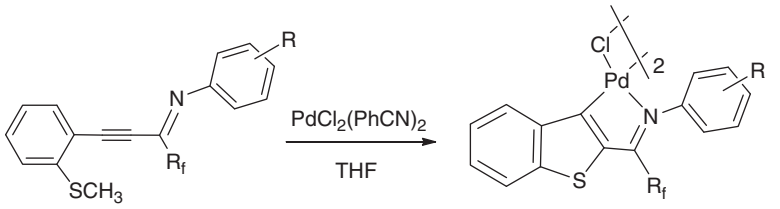


Scheme 37

Nucleophilic addition of sulfur-based nucleophiles to alkynes coordinated to palladium was reported by Likhar et al.[66] They found that treatment of *o*-MeSC$_6$H$_4$C≡CC(R$_f$)(CF$_3$)=N-C$_6$H$_4$R) (**193–195**) with PdCl$_2$(PhCN)$_2$ in THF gave metallacyclic complexes formed by attack of SMe on coordinated alkyne followed by elimination of CH$_3$Cl (Scheme 38).

4.10.2.5 Reactions of Chloride Ion

Nucleophilic attack of chloride ion on coordinated alkynes has been reported for alkyne complexes of Os, Ni, Pd, and Pt.

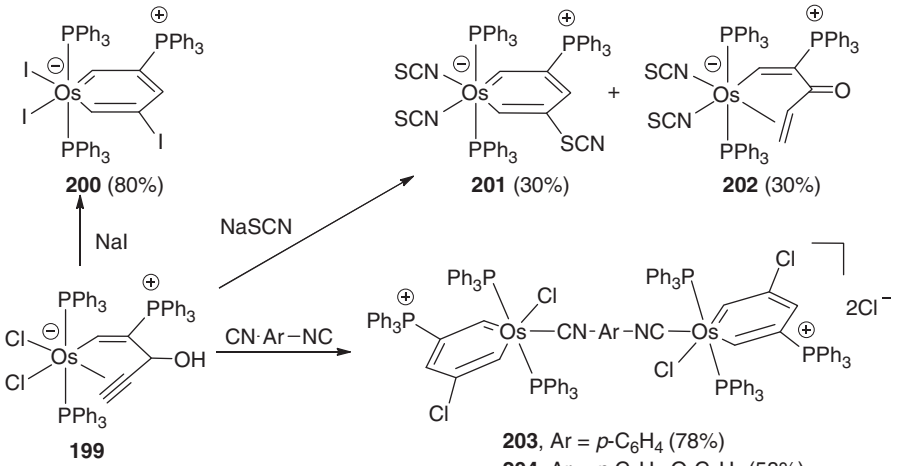


193, R = *p*-OMe; $R_f = CF_3$
194, R = H; $R_f = C_4F_9$
195, R = *o*-OMe, $R_f = CF_3$

196, R = *p*-OMe; $R_f = CF_3$ (62%)
197, R = H; $R_f = C_4F_9$ (65%)
198, R = *o*-OMe, $R_f = CF_3$ (79%)

Scheme 38

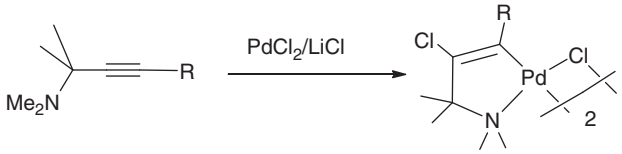
Addition of halides to alkyne ligands coordinated to osmium was observed in the reactions of the alkyne complex **199** with halide salts. The complex reacted with NaI and NaSCN to give the osmabenzene complexes **200** and **201**, respectively (Scheme 39).[67] It also reacted with NaCl in the presence of diisocyanides and NH_4PF_6 to give the bisosmabenzenes **203–206** containing a chloro and a phosphonium substituent.[68]



203, Ar = *p*-C_6H_4 (78%)
204, Ar = *p*-C_6H_4-O-C_6H_4 (58%)
205, Ar = *p*-C_6H_4-C_6H_4 (71%)
206, Ar = *p*-C_6H_4-CH_2-C_6H_4 (68%)

Scheme 39

A number of examples of nucleophilic addition of the chloride ion to C≡C bonds of hetero-substituted alkynes coordinated to group 10 metals have been documented. The first example of such reaction was reported in 1968, which involves the reactions of the propargyl amines $RC{\equiv}CCMe_2NMe_2$ (**207**, R=H; **208**, R=Ph) with palladium chloride in the presence of lithium chloride to give the corresponding five-membered metallacycles (**209** and **210**) (Scheme 40).[69] The structure of **209** was confirmed by X-ray diffraction in 1995.[70]



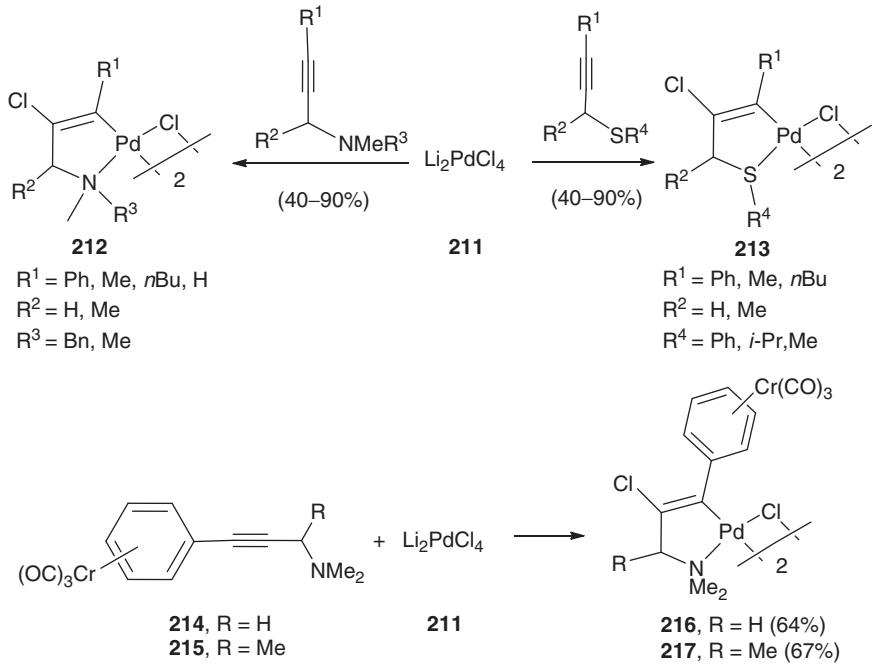
207, R = H
208, R = Ph

209, R = H (27%)
210, R = Ph (95%)

Scheme 40

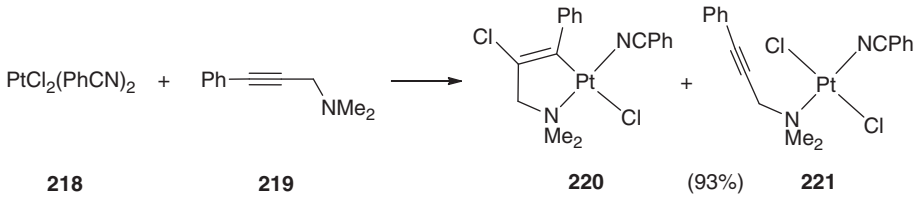
The reaction has been extended to prepare palladacycles from other propargyl amines and thioethers.[71,72] For example, the propargyl amines $R^1C{\equiv}CCH(R^2)NMe(R^3)$ and thioethers $R^1C{\equiv}CCH(R^2)SR^4$ (R^1=Me, *n*Bu, Ph; R^2=H, Me; R^3=Me, Bn; and

R^4 = Me, *i*-Pr, Ph) reacted with Li_2PdCl_4 (**211**) in methanol to give five-membered palladacyclic compounds **212** and **213**, respectively (Scheme 41). Similarly, $Me_2NCH(R)C{\equiv}CPh[Cr(CO)_3]$ (**214**, R = H; **215**, R = Me) reacted with Li_2PdCl_4 to produce the metallacyclic complexes **216** and **217**.[73]



Scheme 41

When $PtCl_2(PhCN)_2$ was treated with $PhC{\equiv}CCH_2NMe_2$, the reaction produced a mixture of complexes **220** (formed by chloroplatination) and **221** (formed by simple ligand substitution) (Scheme 42).[74]



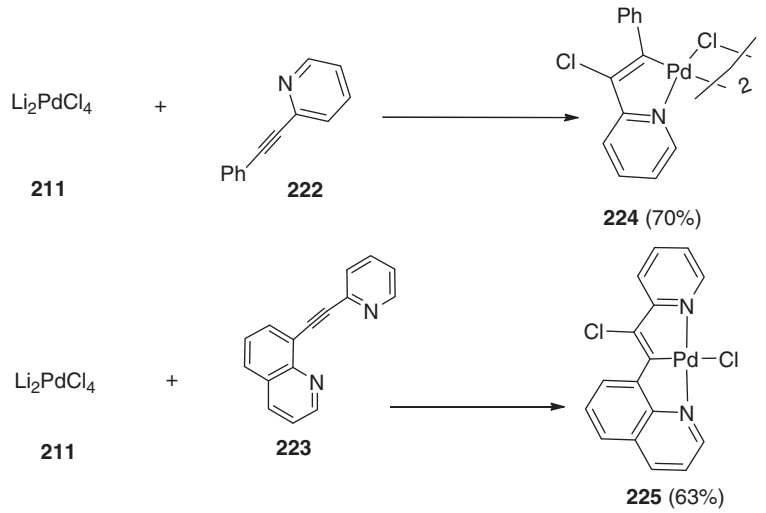
Scheme 42

Alkynes with a pyridyl substituent can react similarly. For example, Li_2PdCl_4 (**211**) reacted with phenyl-2-pyridinyl-acetylene (**222**) to give the five-membered palladacycle **224** (Scheme 43).[75] The reaction of 2-pyridinyl-8-quinolinyl-acetylene (**223**) with Li_2PdCl_4 afforded the pincer palladacycle **225**, which is emissive in both solution and the solid state.

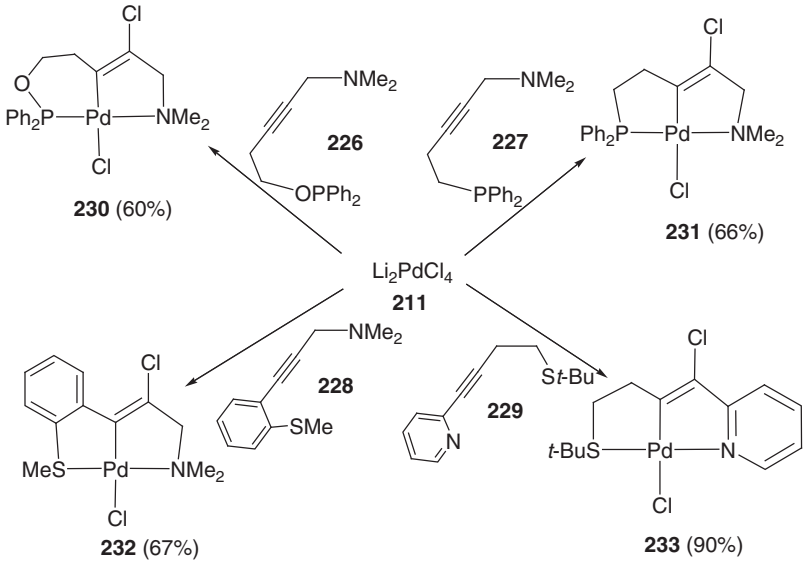
The reaction has been used to prepare unsymmetrical 'pincer' palladium complexes of the type of (XCX′)PdCl (X, X′ = NR_2, Py, PPh_2, $OPPh_2$, $OP(iPr)_2$, and SR).[76] For example, Li_2PdCl_4 (**211**) reacted with hetero-substituted alkynes $Me_2NCH_2C{\equiv}CCH_2$-CH_2OPPh_2 and $Me_2NCH_2C{\equiv}CCH_2CH_2PPh_2$ to give complexes **230** and **231**, respectively; and with *o*-$MeSC_6H_4C{\equiv}CCH_2NMe_2$ and *o*-$NC_5H_4C{\equiv}CCH_2CH_2S$-*t*Bu to yield the pincer complexes **232** and **233**, respectively (Scheme 44).

Nucleophilic attack of chloride ion on alkyne coordinated to nickel has also been used to prepare pincer nickel complexes of *N*-heterocyclic carbenes. For example, the reactions of the silver complexes **234** and **235** with $NiCl_2(PPh_3)_2$ in acetonitrile produced complexes **236** and **237**, respectively (Scheme 45).[77]

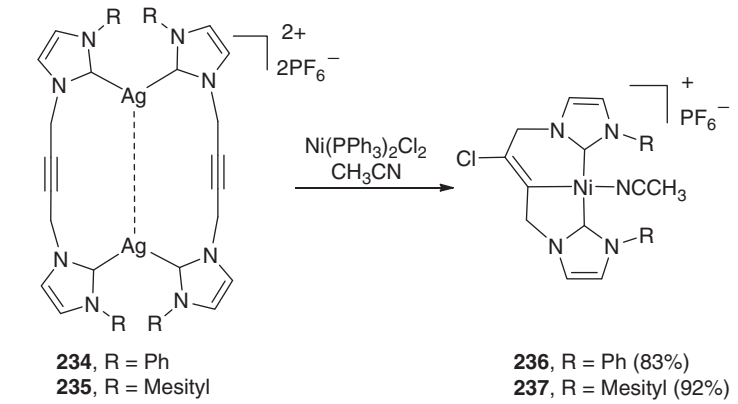
Compared to chlorometalation of hertero-substituted alkynes, reported chlorometalation reactions involving simple alkynes are limited. As rare examples, the reaction of *trans*-PtX(Me)$(PMe_2Ph)_2$ (X = C1, Br, I) with $RC{\equiv}CCOOMe$ (R = COOMe, Ph, Me, H) in the presence of HCl affords *trans*-PtX{C(COOMe)=C(Cl)R}$(PMe_2Ph)_2$ (Scheme 46).[58]



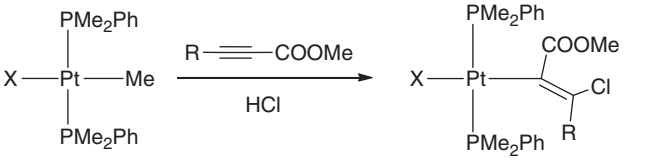
Scheme 43



Scheme 44



Scheme 45



147, X = Cl
238, X = Br
239, X = I

240, X = Cl; R = COOMe
241, X = Cl; R = Ph
242, X = Cl; R = Me
243, X = Cl; R = H
244, X = Br; R = COOMe
245, X = I; R = COOMe

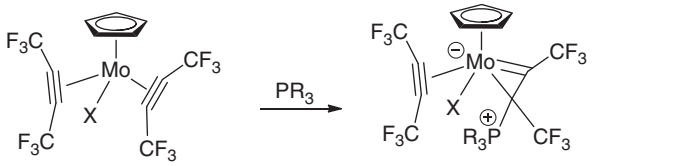
Scheme 46

4.10.2.6 Reactions of Phosphorus-Based Nucleophiles

Phosphines and phosphites are commonly used ligands in coordination chemistry and catalysis. They can also function as nucleophiles to attack on coordinated unsaturated substrates. Nucleophilic addition of phosphines and phosphites to coordinated alkyne ligands has been reported for alkyne complexes of group 6–8 metals.

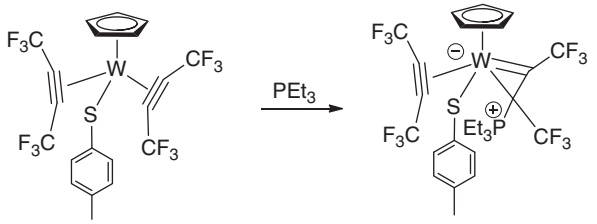
4.10.2.6.1 Reactions of group 6 metal complexes

It has been reported that phosphines or phosphites can add to alkyne ligands coordinated to Mo(II) and W(II) centers to give η^2-vinyl complexes. For example, the molybdenum and tungsten complexes $CpMX(CF_3C{\equiv}CCF_3)_2$ (**79**, M = Mo, X = Cl; **246**, M = Mo, X = SC_6F_5; **255**, M = W, X = S(*p*-C_6H_4Me)) undergo nucleophilic attack by the phosphorus lone pair of phosphites and phosphines to give the corresponding η^2-vinyl complexes (Scheme 47). A similar reaction occurred between $WBr_2(CO)(CF_3C{\equiv}CF_3)_2$ (**257**) and $P(OMe)_3$ to give the η^2-vinyl complex **258**.[22,78]

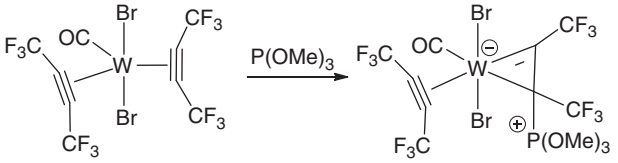


79, X = Cl
246, X = SC_6F_5

247, X = Cl, PR_3 = PEt_3
248, X = Cl, PR_3 = PMe_2Ph
249, X = Cl, PR_3 = PPh_3
250, X = Cl, PR_3 = $P(OMe)_3$
251, X = SC_6F_5, PR_3 = PEt_3
252, X = SC_6F_5, PR_3 = PMe_2Ph
253, X = SC_6F_5, PR_3 = PPh_3
254, X = SC_6F_5, PR_3 = $P(OMe)_3$



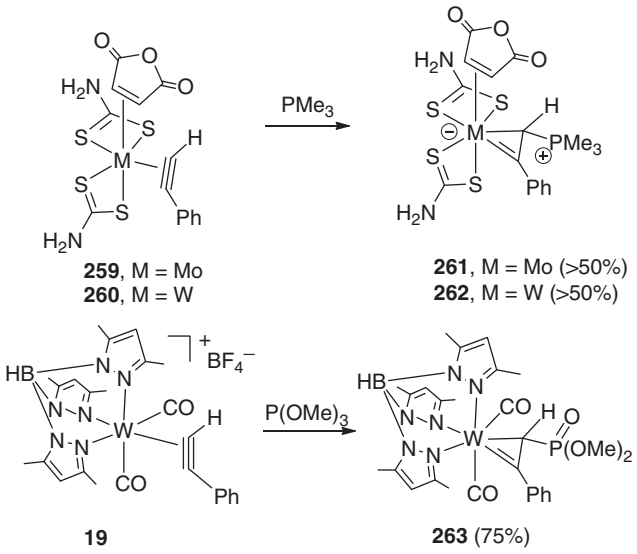
255 **256**



257 **258**

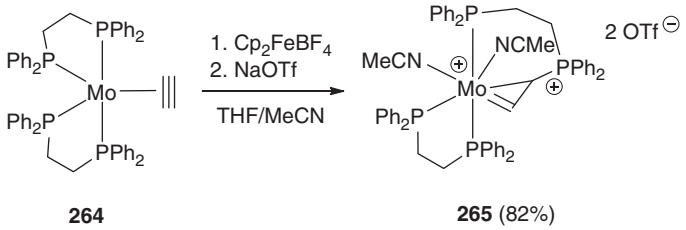
Scheme 47

Terminal alkyne ligands coordinated to Mo(II) and W(II) centers can be attacked by phosphines or phosphites regioselectively at the terminal alkyne-carbon to give η^2-vinyl complexes. For example, the reactions of the alkyne complexes **259** and **260** with PMe_3 produce the η^2-vinyl complexes **261** and **262**, respectively,[79] the reaction of the TpW complex **19** with $P(OMe)_3$ gave the P(O)$(OMe)_2$ substituted η^2-vinyl complex **263** (Scheme 48).[19]



Scheme 48

A coordinated alkyne ligand can even be attacked by chelating phosphines. For example, treatment of *trans*-Mo(HC≡CH)$(dppe)_2$ (**264**) (dppe=$Ph_2PCH_2CH_2PPh_2$) with $[Cp_2Fe]BF_4$ in THF-MeCN followed by anion metathesis with NaOTf produced the unusual η^2-vinyl complex $[Mo(\eta^2\text{-}CHCHPPh_2CH_2CH_2PPh_2)(MeCN)_2(dppe)](OTf)_2$ (**265**), because of nucleophilic attack of a phosphorus atom in the dppe ligand on the alkyne-carbon (Scheme 49).[80]



Scheme 49

Nucleophilic attack of phosphines on coordinated alkynes also occurred in the reactions of alkynes with Mo(IV) complexes $MoH\{S(2,4,6\text{-}C_6H_2R_3)\}_3(PMePh_2)$ (R=Me or *i*Pr) and $MoH\{S(2,4,6\text{-}C_6H_2(iPr)_3\}_3(PMe_2Ph)_2$. For example, treatment of $MoH\{S(2,4,6\text{-}C_6H_2(iPr)_3)\}_3(PMePh_2)$ (**266**) with HC≡CPh in tetrahydrofuran-MeOH gave the alkenyl complexes **267** (the source of the oxide ligand is adventitious water) (Scheme 50), treatment of $MoH\{S(2,4,6\text{-}C_6H_2(iPr)_3\}_3(PMe_2Ph)_2$ with HC≡CPh under similar condition gave the phosphonium-alkylidene complex **269**.[81]

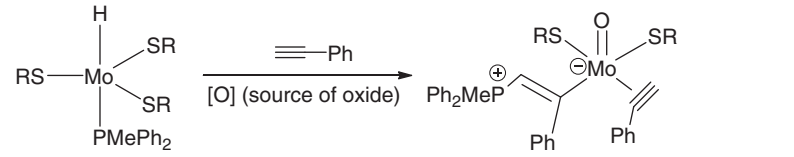
4.10.2.6.2 Reactions of group 7 metal complexes

Several examples of nucleophilic addition of phosphines to alkyne ligands coordinated to group 7 metals such as Mn and Re have been reported.

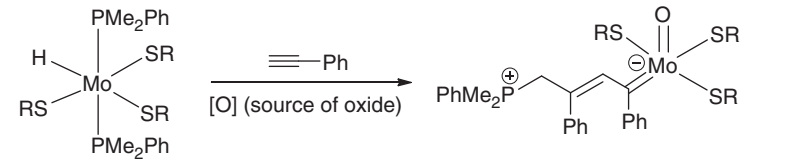
The Mn(I) complex $CpMn(CO)_2(HC{\equiv}CCO_2Me)$ (**270**) reacted with PPh_3 and dppe to give the alkenyl complexes **271** and **272**, respectively (Scheme 51).[82]

Addition of phosphines to alkynes coordinated to Re(II) and Re(V) centers are also known. Scheme 52 shows examples of reactions involving Re(II) complexes. The formally Re(II) dinuclear terminal alkyne complexes **273** reacted with a variety of phosphines to give the corresponding alkenyl complexes **274**.[83]

Scheme 53 shows examples of reactions involving Re(V) complexes. The rhenium(V) alkyne complex **276**, prepared by the reaction of **275** with HC≡CH, rearranged readily in solution to give the vinylalkylidene complex $Re(NAr)_2(CH_2CMe_3)$ $(CHCHPMe_2Ph)$ (**277**) (Scheme 54).[84] The cationic rhenium(V) complexes containing HC≡CH (**278**) or PhC≡CH (**279**)

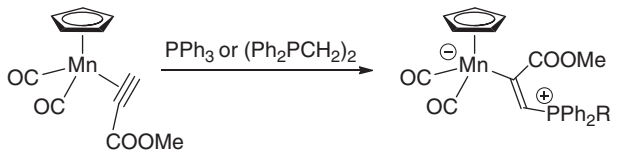


266, R = 2,4,6-$C_6H_2(i\text{Pr})_3$ **267**, R = 2,4,6-$C_6H_2(i\text{-Pr})_3$ (47%)



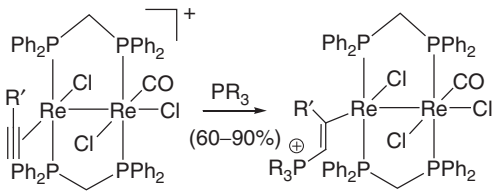
268, R = 2,4,6-$C_6H_2(i\text{-Pr})_3$ **269**, R = 2,4,6-$C_6H_2(i\text{-Pr})_3$ (83%)

Scheme 50



270 **271**, R = Ph
272, R = $CH_2CH_2PPh_2$

Scheme 51



273 **274**

R′ = H, *n*Pr, *n*Bu, Ph
PR_3 = PEt_3, $PMePh_2$, PMe_3, PMe_2Ph

Scheme 52

readily reacted with phosphines to give the corresponding alkenyl complexes (e.g., **280–282**).[85] It is interesting to note that the phosphines attacked the substituted alkyne-carbon in the reaction of the phenylacetylene complex **279** with PMe_3.

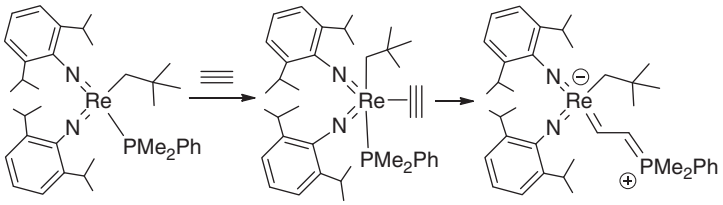
Nucleophilic attack of phosphines on coordinated alkynes also occurred in the reactions of alkynes with Re(V)-phosphine complexes. For example, the reaction of Re(O)$(CH_2SiMe_3)_3(PMe_3)$ (**283**) with excess HC≡CH produced the alkenyl complex Re(O)$(CH_2SiMe_3)_3(CH{=}CHPMe_3)$ (**285**) (Scheme 54),[86,87] the reaction of Re(O)Cl$(Me)_2(PMe_2Ph)_2$ (**287**) with excess HC≡CH gave the alkenyl complex Re(O)Cl$(Me)_2(CH{=}CHPMe_2Ph)_2$ (**289**),[87] reaction of Re(O)$Cl_3(PPh_3)_2$ (**291**) with HC≡CPh yielded the alkenyl complex Re(O)$Cl_3(PPh_3)(PhC{=}CHPPh_3)$ (**292**).[88]

Reactions of $ReOCl_2(OEt)(PPh_3)_2$ (**293**) with both terminal and internal alkynols lead to phosphine addition alkenyl products. In general, the phosphine adds to the terminal carbon of terminal alkynols, and to the alkyne-carbon closer to the OH group of internal alkynols, as illustrated by the two examples shown in Scheme 55.[89]

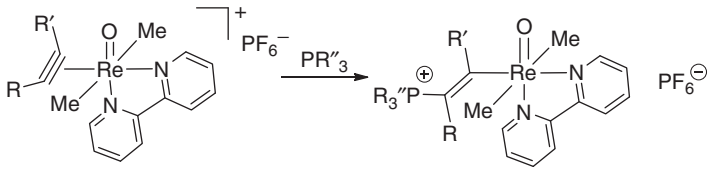
4.10.2.6.3 Reactions of group 8 metal complexes

Scheme 56 shows examples of addition of phosphines to alkynes coordinated to a Ru(II) center. Treatment of the indenyl ruthenium-alkyne complexes $[(\eta^5\text{-}C_9H_3R'_3)Ru(HC{\equiv}CPh)(CO)(PR_3)]BF_4$ (**296**, $PR_3{=}PPh_3$; **297**, $PR_3{=}P(i\text{-Pr})_3$) with PPh_3 produced the alkenyl complexes $[(\eta^5\text{-indenyl})Ru\{HC{=}CPh(PPh_3)\}(CO)(PR_3)]BF_4$ (**298**, $PR_3{=}PPh_3$; **299**, $PR_3{=}P(i\text{-Pr})_3$).[90]

Attacking of phosphine on coordinated alkynes occurred in the protonation reactions of ruthenium alkynyl complexes TpRu(C≡CR)X(NO) (X=Cl, C≡CR) with HBF_4 in the presence of PPh_3.[91,92] For example, the alkynyl complex **300** reacted with



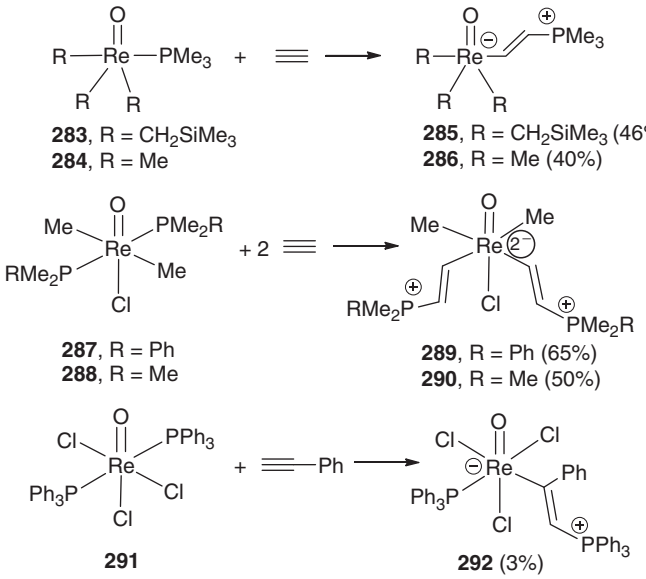
275 **276** **277** (55%)



278, R = R′ = H
279, R′ = H; R′ = Ph

280, R = R′ = H; PR″$_3$ = PMe$_3$ (45%)
281, R = R′ = H; PR″$_3$ = PPh$_3$ (62%)
282, R = Ph; R′ = H; PR″$_3$ = PMe$_3$ (90%)

Scheme 53



283, R = CH_2SiMe_3
284, R = Me

285, R = CH_2SiMe_3 (46%)
286, R = Me (40%)

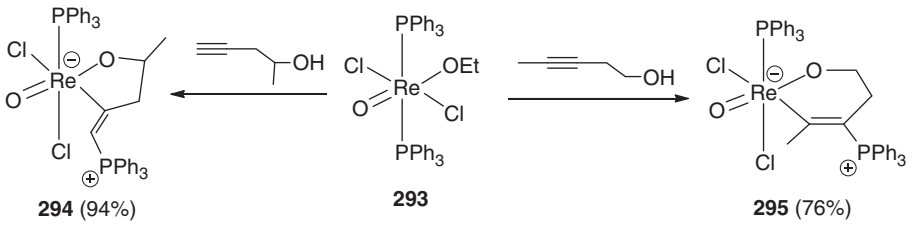
287, R = Ph
288, R = Me

289, R = Ph (65%)
290, R = Me (50%)

291

292 (3%)

Scheme 54



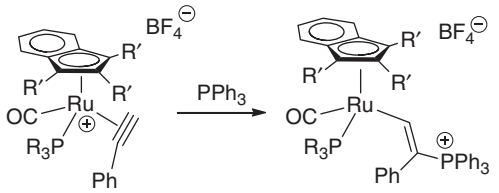
294 (94%)

293

295 (76%)

Scheme 55

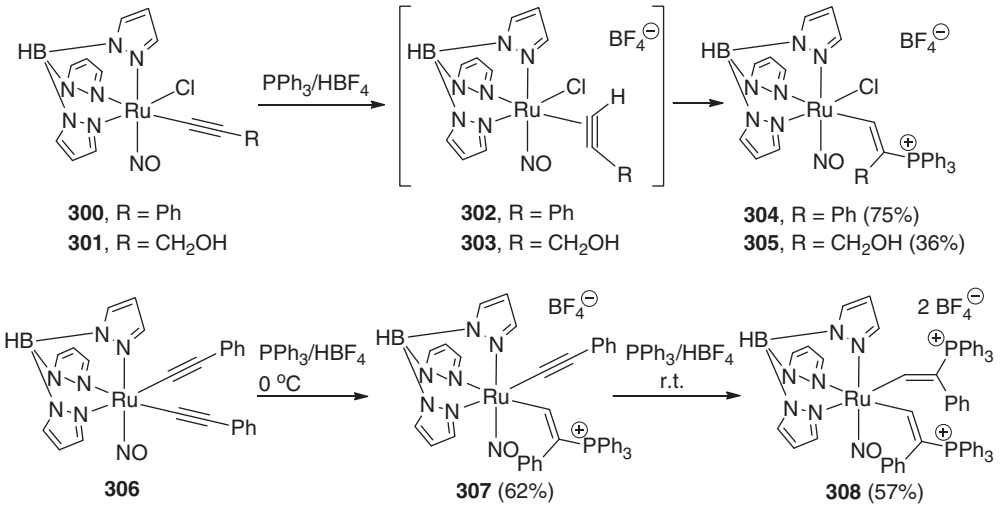
HBF_4 in the presence of PPh_3 to give the alkenyl complex **304** via η^2-alkyne complex **302**; the bisalkynyl complex **306** reacted with PPh_3 in the presence of HBF_4 to give the monocationic alkenyl complex **307** and then the dicationic alkenyl complex **308** (Scheme 57).



296, R = Ph, R′ = Me
297, R = *i*-Pr ,R′ = H

298, R = Ph, R′ = Me (60%)
299, R = *i*-Pr, R′ = H (70%)

Scheme 56



300, R = Ph
301, R = CH_2OH

302, R = Ph
303, R = CH_2OH

304, R = Ph (75%)
305, R = CH_2OH (36%)

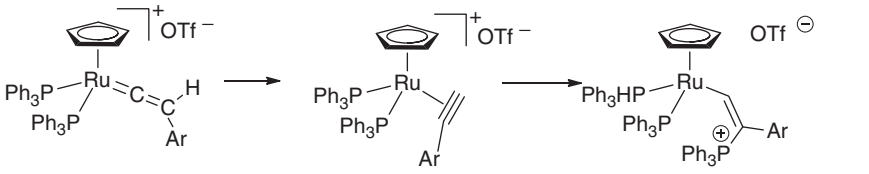
306

307 (62%)

308 (57%)

Scheme 57

Nucleophilic attack of phosphine on coordinated alkynes is responsible for the formation of alkenyl complexes in the reactions of phosphines with ruthenium vinylidene complexes $[CpRu(=C=CRR')(PR_3)_2]^+$, which can rearrange to η^2-alkyne complexes. For example, the vinylidene complexes **309** and **310** reacted with PPh_3 to give the alkenyl complexes **313** and **314**, respectively (Scheme 58).[93,94]



309, Ar = Ph
310, Ar = *m*-C_6H_3OMe

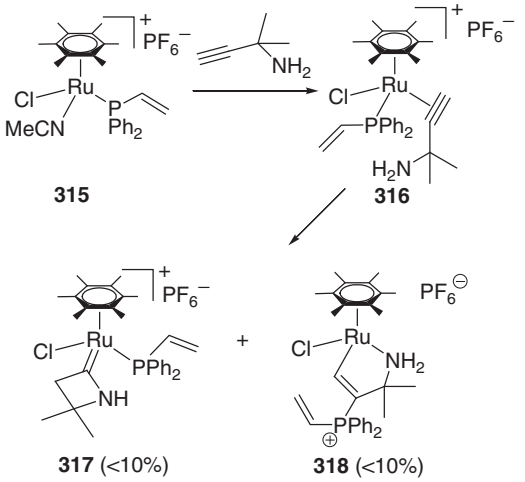
311, Ar = Ph
312, Ar = *m*-C_6H_3OMe

313, Ar = Ph (77%)
314, Ar = *m*-C_6H_3OMe (69%)

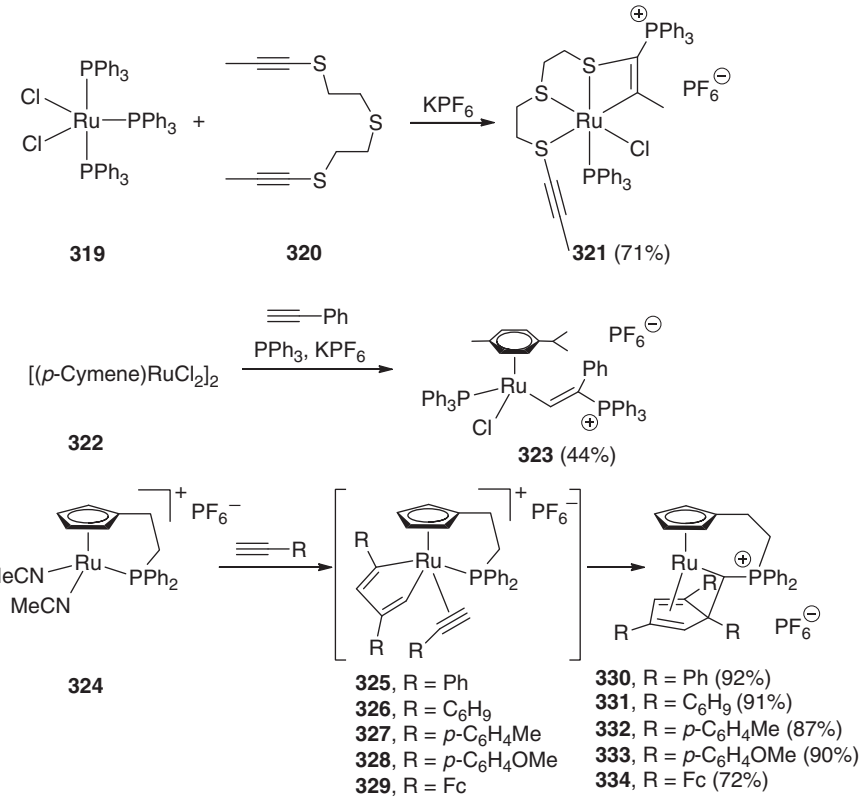
Scheme 58

Nucleophilic attack of phosphine on coordinated alkynes may also occur when a ruthenium–phosphine complex is treated with alkynes. For example, treatment of the ruthenium complex **315** with $HC{\equiv}CCMe_2NH_2$ gave a mixture of the amino cyclic carbene complex **317** and the metallacyclic complex **318** (Scheme 59).[95] The latter complex is formed through intermediate **316** by nucleophilic attack of the coordinated phosphine.

As additional examples of addition of phosphines to alkynes coordinated to ruthemium, $RuCl_2(PPh_3)_3$ (**319**) reacted with α,ω-diyne 4,7,10-trithiatrideca-2,11-diyne (**320**) and KPF_6 to form the phosphonio-substituted metallatricyclic complex **321** arising from nucleophilic attack of extraneous phosphine on one of the alkynyl group (Scheme 60).[96] [(*p*-Cymene)$RuCl_2(PPh_3)$] (**322**) reacted with phenylacetylene and PPh_3 in the presence of KPF_6 to produce the alkenyl complex **323**.[97,98] Furthermore, treatment of the ruthenium complex **324** with terminal alkynes produced η^4-diene complexes (e.g., **330**–**334**), which were presumably formed by initial nucleophilic attack of the pendant phosphine ligand at the coordinated acetylene of the metallacyclopentadiene intermediates (e.g., **325**–**329**) followed by C–C coupling.[99]



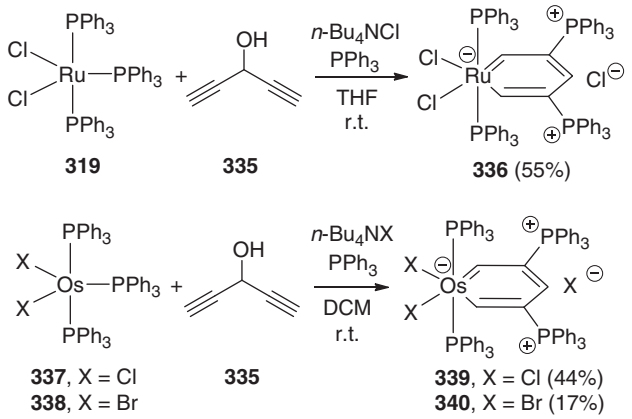
Scheme 59



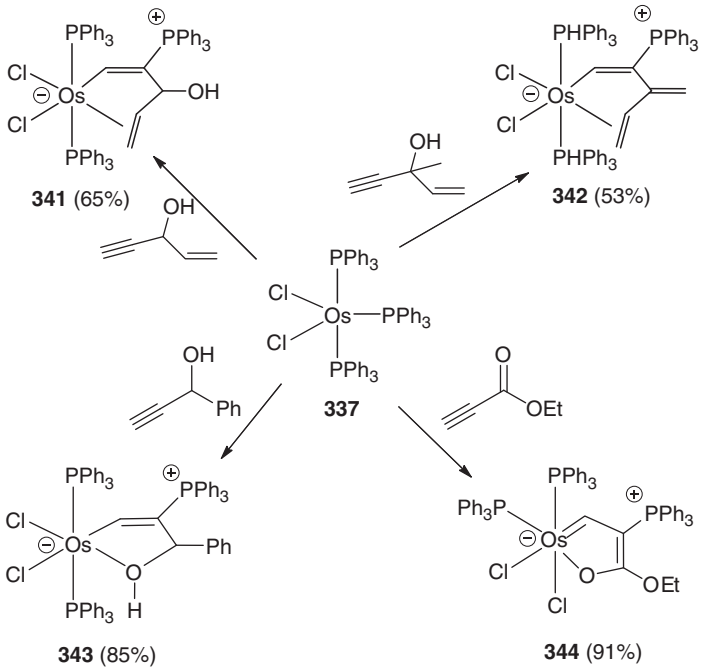
Scheme 60

Nucleophilic attack of phosphines on coordinated alkynols has been used to prepare metallabenzenes. For example, treatment of $RuCl_2(PPh_3)_3$ (**319**) with HC≡CCH(OH)C≡CH (**335**) in the presence of PPh_3 and Bu_4NCl at room temperature produced the ruthenabenzene **336**,[100,101] the reaction of $OsCl_2(PPh_3)_3$ (**337**) with HC≡CCH(OH)C≡CH in the presence of PPh_3 and Bu_4NCl produced the osmabenzene **339**. The reaction of $OsBr_2(PPh_3)_3$ (**338**) with HC≡CCH(OH)C≡CH in the presence of PPh_3 and Bu_4NBr produced the analogous osmabenzene complex **340** (Scheme 61).[67]

Nucleophilic attacking of phosphines on coordinated alkynes was also observed in the reactions of $OsCl_2(PPh_3)_3$ (**337**) with other alkynes. For example, the reactions of $OsCl_2(PPh_3)_3$ with HC≡CCH(OH)CH=CH_2 and HC≡CCMe(OH)CH=CH_2 produced the alkenyl complexes **341**[102] and **342**,[103] respectively (Scheme 62). Treatment of $OsCl_2(PPh_3)_3$ (**337**) with HC≡CCH(OH)Ph and HC≡CCOOEt gave the metallacyclic complexes **343**[104] and **344**,[105] respectively.



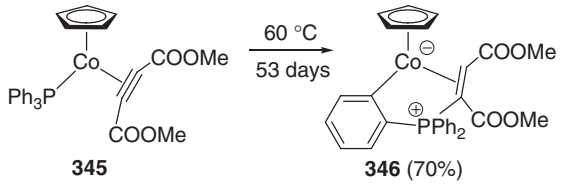
Scheme 61



Scheme 62

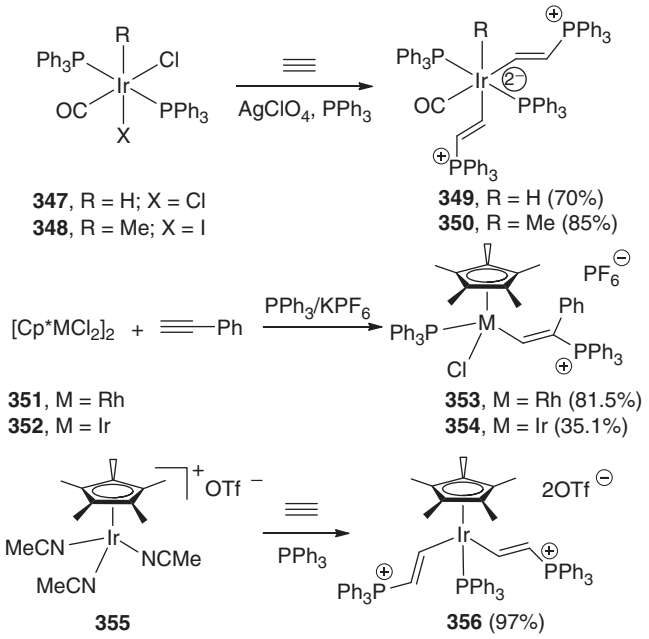
4.10.2.6.4 Reactions of group 9 metal complexes

Several examples of nucleophilic addition of phosphines to alkynols coordinated to group 9 metals Co and Ir have been documented. Attacking on the alkyne MeOOCC≡CCOOMe by PPh_3 occurred in the thermolysis of the η^2-alkyne complex CpCo(PPh_3)(MeOOCC≡CCOOMe) (**345**). The reaction produced the *ortho*-metalated vinyl-phosphonium derivative **346** (Scheme 63).[106]



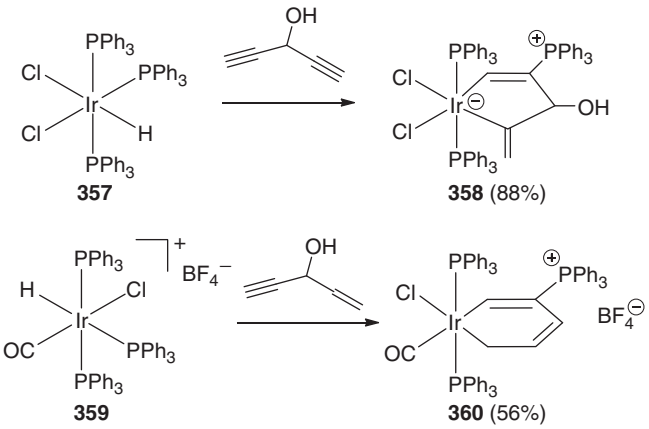
Scheme 63

Nucleophilic attack of phosphine on alkynes coordinated to iridium was observed in the reactions of some iridium(III) complexes with alkynes. For example, the dihaloiridium(III) complexes $IrRClX(CO)(PPh_3)_2$ (**347**, X=Cl, R=H; **348**, X=I, R=Me) reacted with $HC{\equiv}CH/PPh_3$ in the presence of $AgClO_4$ to produce *cis*-bis(alkenyl)iridium complexes **349** and **350**,[107] $[Cp^*MCl_2]_2$ (**351**, M=Rh; **352**, M=Ir) reacted with phenylacetylene and PPh_3 in the presence of KPF_6 to yield the alkenyl complexes $[Cp^*MCl(CH{=}CHPPh_3)(PPh_3)]PF_6$ (**353**, M=Rh; **354**, M=Ir),[97,98] $[Cp^*Ir(NCMe)_3](OTf)_2$ (**355**) reacted with $HC{\equiv}CH$ and PPh_3 to give the vinyl complex **356** (Scheme 64).[108]



Scheme 64

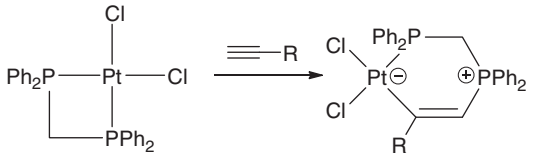
Nucleophilic addition of phosphine to coordinated alkynes has also been used to prepare interesting iridacycles. For example, treatment of *cis*-$IrHCl_2(PPh_3)_3$ (**357**) with $HC{\equiv}CCH(OH)C{\equiv}CH$ in dichloromethane led to the formation of the metallacycle **358** (Scheme 65),[109] treatment of $[IrHCl(CO)(PPh_3)_3]BF_4$ (**359**) with $HC{\equiv}CCH(OH)CH{=}CH_2$ afforded the iridacyclohexadiene **360**.[110]



Scheme 65

4.10.2.6.5 Reactions of group 10 metal complexes

Addition of phosphine to alkyne coordinated to palladium was observed in the reactions of $PdCl_2$(dppm) (**361**) with terminal arylacetylenes. These reactions generated six-membered metallacycles (e.g., **362**–**365**) (Scheme 66).[111]



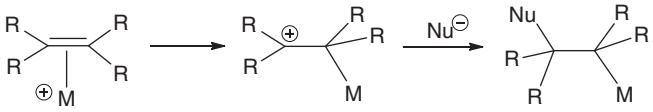
361

362, R = Ph (49%)
363, R = *n*-C_9H_{19} (48%)
364, R = *p*-$PhNMe_2$ (31%)
365, R = *p*-$PhNO_2$ (73%)

Scheme 66

4.10.3 Reactions of Alkenes

Nucleophilic addition to coordinated alkenes have been studied extensively both experimentally and theoretically. Theoretical studies suggest that the reaction could proceed by initial rearrangement of the η^2-alkene ligand to an η^1-ligand followed by nucleophilic addition (Scheme 67),[112] although direct nucleophilic attack on the double bond may also be possible. As will be presented below (see Sections 4.10.3.1–4.10.3.5), numerous examples of nucleophilic addition to coordinated alkenes have been demonstrated experimentally, especially for middle/late transition metals.



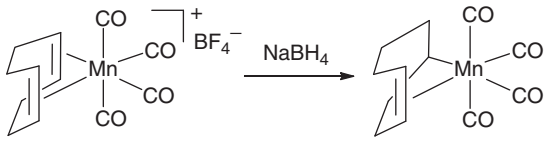
Scheme 67

4.10.3.1 Reactions of Hydride and Carbon-Based Nucleophiles

Nucleophilic addition of hydride and carbon-based nucleophiles to coordinated alkene ligands has been reported for well-defined alkene complexes of group 7–10 metals.

4.10.3.1.1 Reactions of group 7 metal complexes

Limited examples are known for the nucleophilic addition reactions of hydride or carbon-based nucleophiles with group 7 metal–alkene complexes. As a rare example, treatment of $[Mn(CO)_4(COD)]BF_4$ (**366**) with $NaBH_4$ produced the enyl complex **367** (Scheme 68).[113]



366 **367**

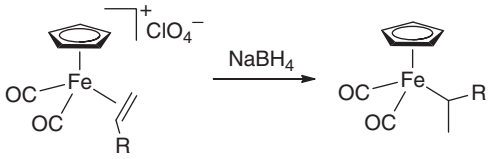
Scheme 68

4.10.3.1.2 Reactions of group 8 metal complexes

The first example of nucleophilic addition of hydride to alkenes coordinated to iron was reported by Green and Nagy in 1962. They found that the complexes $[CpFe(CH_2{=}CHR)(CO)_2]ClO_4$ (**368**, R=H; **369**, R=Me) reacted with $NaBH_4$ to give the alkyl complexes $CpFe(CH_3CHR)(CO)_2$ (**370**, R=H; **371**, R=Me) (Scheme 69).[114]

Nichloas and Floro reported in 1975 that sodium cyanoborohydride is superior to $NaBH_4$ for the conversion of Fe(η^2-alkene) complexes to alkyl complexes.[115] Thus a series of iron complexes of the type $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ reacted with $NaBH_3CN$ in nitromethane to give the corresponding alkyl complexes within minutes in good yields (Scheme 70). With $NaBD_3CN$, stereospecifically labeled β-deuteroalkyl complexes can be obtained. For example, the *trans*-deuteroacenaphthenyl complex **380** was obtained by treatment of the acenaphthylene complex **379** with $NaBD_3CN$.

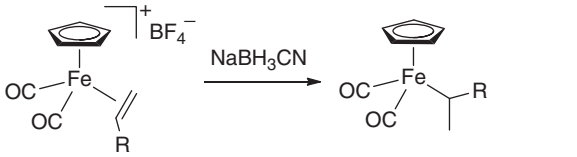
As described by Bodnar et al., even transition metal hydride complexes can effect hydride addition to the olefin ligands of $[CpFe(alkene)(CO)_2]ClO_4$. For example, the ethylene complex $[CpFe(CH_2{=}CH_2)(CO)_2]ClO_4$ (**368**) reacted with CpFeH(CO)



368, R = H
369, R = Me

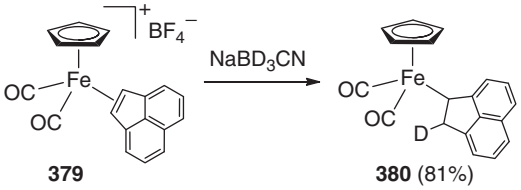
370, R = H
371, R = Me (70%)

Scheme 69



372, R = Me
373, R = Ph
374, R = CH_2Ph
375, R = $(CH_2)_4Me$

371, R = Me (96%)
376, R = Ph (56%)
377, R = CH_2Ph (71%)
378, R = $(CH_2)_4Me$ (81%)

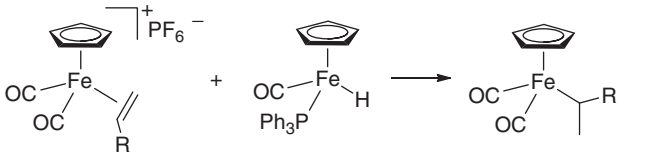


379

380 (81%)

Scheme 70

(PPh_3) (**382**) to give the alkyl complex **370** (Scheme 71).[116] The mono-substituted alkene complexes $[CpFe(CH_2{=}CHR)(CO)_2]ClO_4$ (**369**, R=Me; **381**, R=OMe) reacted with $CpFeH(CO)(PPh_3)$ (**382**) regioselectively at the substituted olefinic carbon to give the corresponding alkyl complexes (**371**, **383**).



368, R = H
369, R = Me
381, R = OMe

382

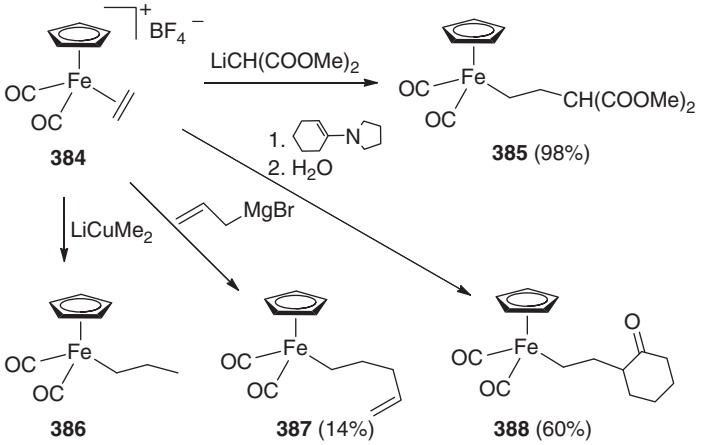
370, R = H (90%)
371, R = Me (90%)
383, R = OMe

Scheme 71

Addition reactions of carbon-based nucleophiles with complexes $[CpFe(alkene)(CO)_2]BF_4$ have been reported by Rosenblum, Sanders, and Nicholas.[117–120] The simplest alkene complex $[CpFe(CH_2{=}CH_2)(CO)_2]BF_4$ (**384**) reacted with $LiCH(COOMe)_2$, $LiCuMe_2$, and $CH_2{=}CHCH_2MgBr$ to produce the alkyl complexes **385**, **386**, and **387**, respectively. The complex $[CpFe(CH_2{=}CH_2)(CO)_2]BF_4$ (**384**) also reacted with 1-(cyclohex-1-enyl)pyrrolidine followed by treatment with water to give the alkyl complex **388** (Scheme 72).

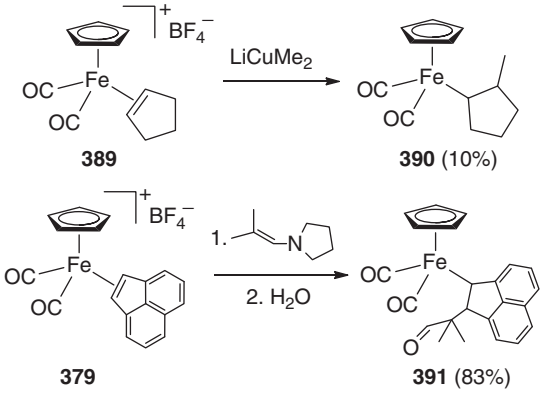
There are experimental evidences that the addition reaction proceeds stereospecifically to give *trans*-adducts. For example, the cyclopentene complex **389** reacted with $LiCuMe_2$ to give the alkyl complex **390**,[117] the η^2-acenphthylene complex **379** reacted with isobutyraldehyde prollidine followed by hydrolysis to give the alkyl complex **391** (Scheme 73).[120]

The regioselectivity of the nucleophilic addition reactions of the alkene complexes $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ are dependent on the substituents on the olefins. For example, the reaction of $[CpFe(CH_2{=}CHMe)(CO)_2]BF_4$ (**372**) with $LiCuMe_2$ produced a 1:1 mixture of the alkyl complexes **392** and **393**, the reaction of $[CpFe(CH_2{=}CHPh)(CO)_2]BF_4$ (**373**) with $LiCuMe_2$ produced a 2:1 mixture of the alkyl complexes **394** and **395**, and the reaction of $[CpFe(CH_2{=}CHCHO)(CO)_2]BF_4$ (**396**) with $LiCuMe_2$ produced the alkyl complex **397** as the sole product (Scheme 74).[117]



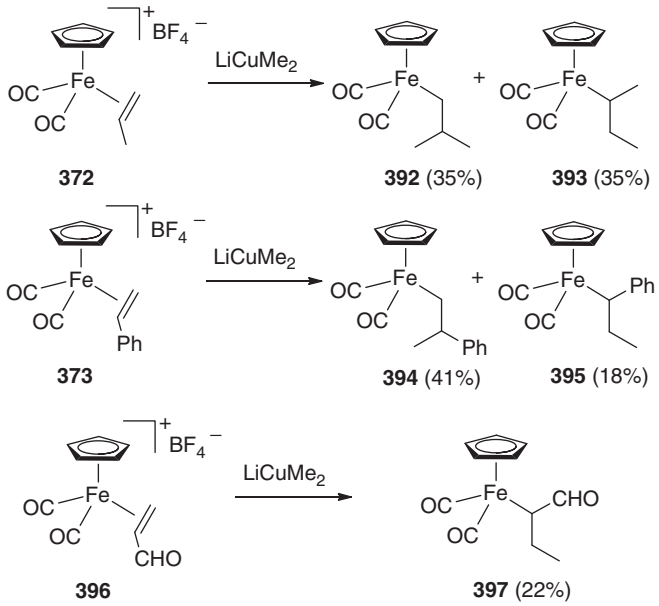
384 **385** (98%) **386** **387** (14%) **388** (60%)

Scheme 72



389 **390** (10%) **379** **391** (83%)

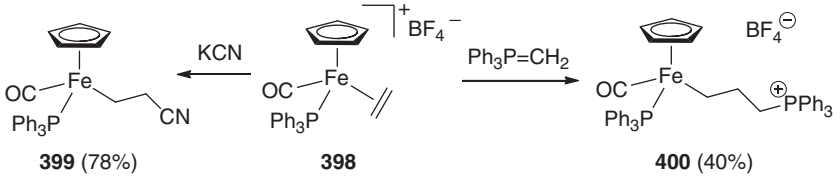
Scheme 73



372 **392** (35%) **393** (35%) **373** **394** (41%) **395** (18%) **396** **397** (22%)

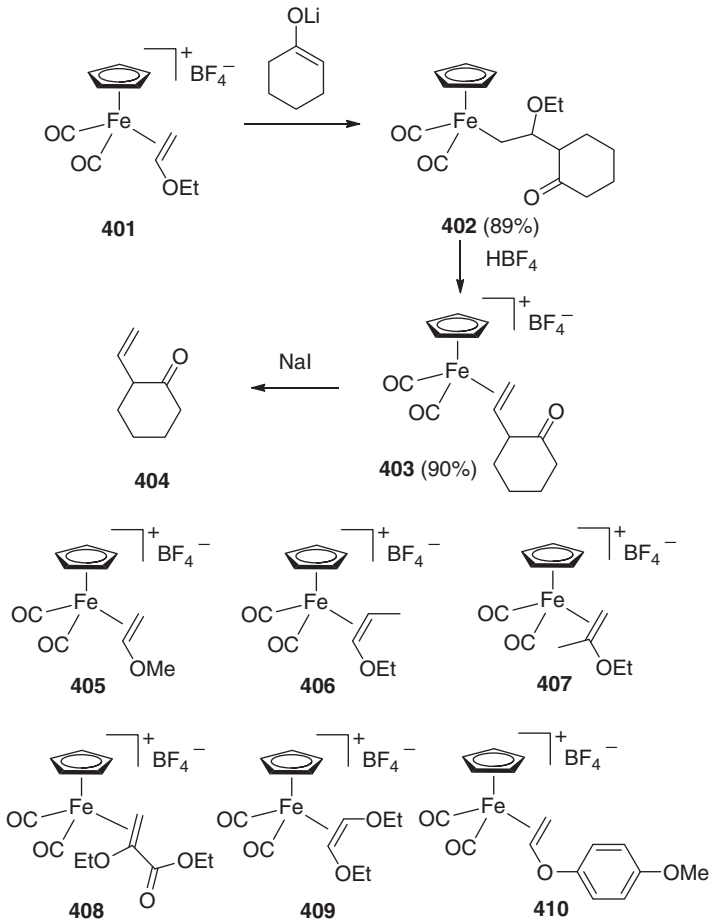
Scheme 74

Nucleophilic addition reactions of $[CpFe(CH_2{=}CH_2)(CO)(PPh_3)]BF_4$ (**398**) have been studied by Reger and Culbertson. They found that the ethylene complex **398** reacted with KCN to give the alkyl complex **399**,[121] and with the ylide $CH_2{=}PPh_3$ to give the alkyl complex **400** (Scheme 75).[122]



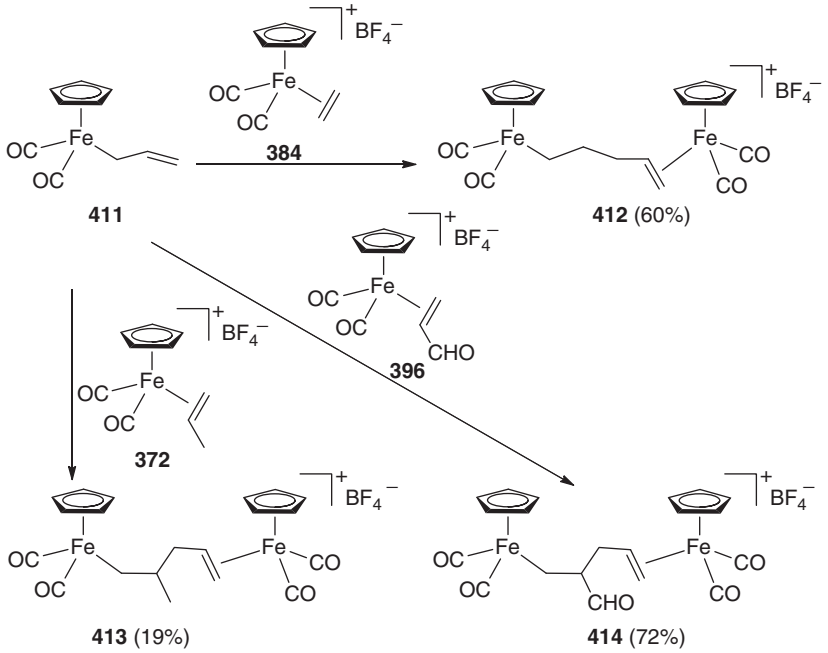
Scheme 75

Rosenblum and coworkers found that vinylether iron complexes $[CpFe(vinylether)(CO)_2]BF_4$ can react with nucleophiles regioselectively at the carbon with an alkoxy substituent and these complexes can be used as a vinyl cation equivalent for organic synthesis. For example, the α-vinylcyclohexanone **404** has been successfully prepared from the organoiron complex $[CpFe(CH_2{=}CHOEt)(CO)_2]BF_4$ (**401**) through the sequence shown Scheme 78.[123] Similar reactions have been reported for other vinylether complexes, for example, complexes **405**–**410** (Scheme 76).[124,125]



Scheme 76

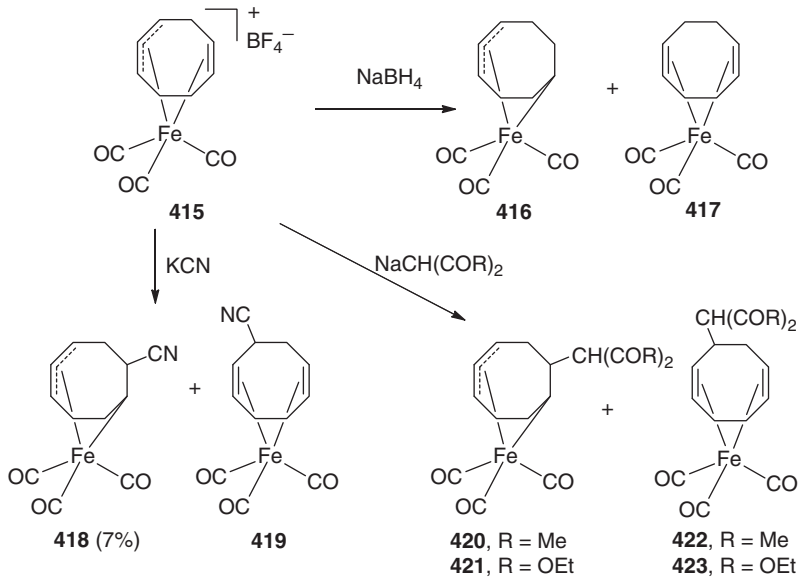
In addition to typical organic nucleophiles, $[CpFe(alkene)(CO)_2]BF_4$ can also be attacked by iron–allyl complexes. For example, the allyl complex $CpFe(CH_2CH{=}CH_2)(CO)_2$ (**411**) reacted with $[CpFe(CH_2{=}CH_2)(CO)_2]BF_4$ (**384**) to give the dinuclear complex **412** (Scheme 77).[126] The allyl complex **411** reacted similarly with the propene complex **372** and the $CH_2{=}CHCHO$ complex **396** to give the bimetallic complexes **413** and **414**, respectively. It has also reported that η^1-allyl iron complexes of the type $CpFe(\eta^1\text{-allyl})(CO)_2$ can undergo [3+2] cycloaddition reactions with acceptors such as $(NC)_2C{=}C(CN)_2$



Scheme 77

(TCNE), dicyanodichloroquinone and methylene malonates. The cycloaddition reactions involve intramolecular nucleophilic addition of a carbanion to a coordinated alkene ligand as one of the elementary steps.[127]

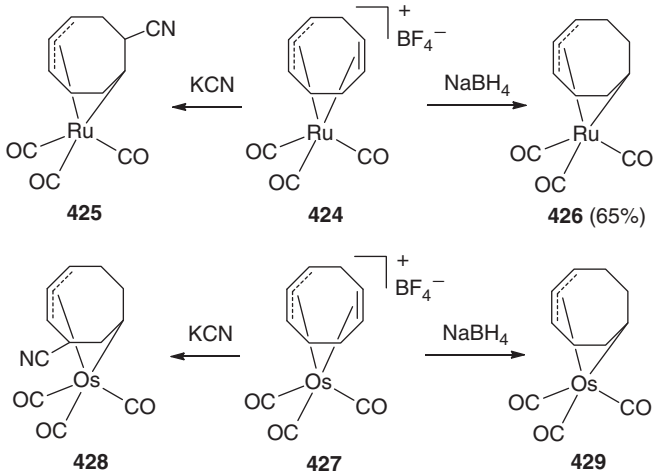
Addition reactions of hydride and carbon-based nucleophiles to group 8 metal complexes containing an η^5-cyclo-octadienenyl ligand have been described by Lewis, Cotton, and Green.[128–131] The η^5-cyclo-octadienenyl iron complex **415** reacted with nucleophilies such as $NaBH_4$, KCN, $NaCH(COMe)_2$, and $NaCH(COOEt)_2$ to give a mixture of two types of complexes, one originated from nucleophilic attack on the allyl ligand, and the other one from nucleophilic attack on the coordinated olefinic ligand (Scheme 78).



Scheme 78

The η^5-cyclo-octadienenyl ruthenium complex **424** reacted with KCN and $NaBH_4$ to give complexes **425** and **426**, respectively, as a result of nucleophilic attack on the coordinated olefinic ligand (Scheme 79). The analogous osmium complex **427** reacted similarly with $NaBH_4$ to give the alkyl complex **429**, but with KCN to give the unexpected addition product **428**.

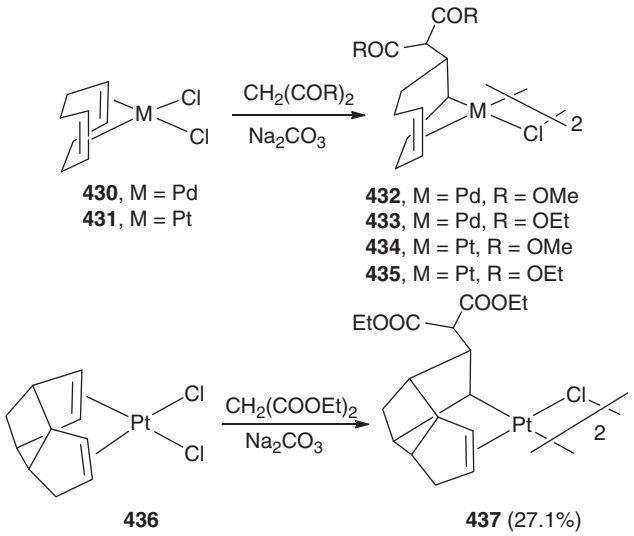
Nucleophilic addition reactions of malonates with iron complexes $[Fe(alkene)(CO)_4]^-$ have also been reported.[132]



Scheme 79

4.10.3.1.3 Reactions of group 10 metal complexes

Attack of carbon-based nucleophiles on alkenes coordinated to group 10 metals was first demonstrated with diene complexes in the late 1960s. The 1,5-cyclooctadiene complexes MCl_2(COD) (**430**, M = Pd; **431**, M = Pt) were reported to readily react with malonates in the presence of Na_2CO_3 to give the dimeric enyl complexes (e.g., **432–435**) (Scheme 80).[133] A similar reaction occurred when $PtCl_2$(endo-dicyclopendiene) was treated with diethylmalonate to give the enyl complex **437**.[134]



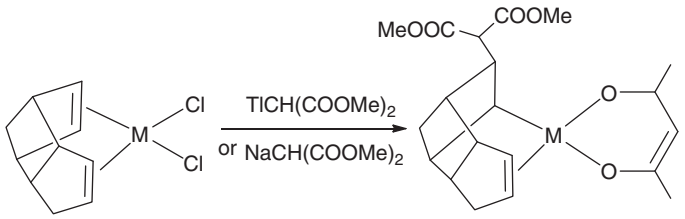
Scheme 80

Dienes coordinated to Pd and Pt can also be attacked by β-diketonates. For example, the dicyclopentadiene complexes MCl_2(dicyclopentadiene) (**436**, M = Pt; **438**, M = Pd) reacted with $TlCH(COOMe)_2$ or $NaCH(COOMe)_2$ to give the enyl complexes **439** and **440** (Scheme 81).[134] Similarly, the COD ligands of MCl_2(COD) (M = Pd, Pt) were attacked by β-diketonates when MCl_2(COD) (M = Pd, Pt) were treated with thallous β-diketonates.[135]

Nucleophilic addition reactions of carbonyl-stabilized phosphorus ylides with diene complexes of palladium and platinum are also known. For example, the palladium complex $PdCl_2$(COD) (**430**) reacted with phosphorus ylides $R_3P{=}CHC(O)R'$(R = Ph, tolyl; R′ = OEt, OMe)[136] to give the corresponding monomeric cyclooctenyl complexes **441–444** (Scheme 82); the platinum complex $PtCl_2$(COD) (**431**) reacted with phosphorus ylides $Ph_3P{=}CHC(O)R$(R = OEt, OMe, NMe_2) to give the corresponding cyclooctenyl complexes **445–447**.

Nucleophilic addition reactions of carbonyl-stabilized phosphorus ylides have also been reported for other platinum-diene complexes as exemplified in Scheme 83.[137]

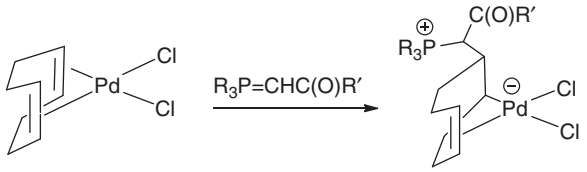
Addition of carbon-based nucleophiles to C–C double bonds of allylic and homoallylic amines and sulfides coordinated to palladium has also been documented. Allylic and homoallylic amines and sulfides undergo carbopalladation reactions with



436, M = Pt
438, M = Pd

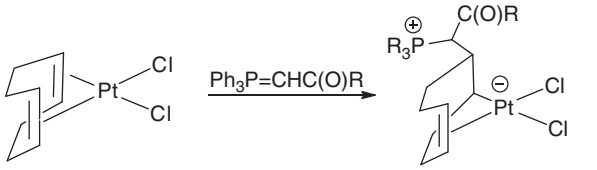
439, M = Pt (2.7%)
440, M = Pd (21.0%)

Scheme 81



430

441, R′ = OMe; R = Ph (74%)
442, R′ = OMe; R = tolyl (70%)
443, R′ = OEt; R = Ph (81%)
444, R′ = OEt; R = tolyl (68%)



431

445, R = OMe (76%)
446, R = OEt (79%)
447, R = NMe_2 (72%)

Scheme 82

Li_2PdCl_4 (**211**) and stabilized enolates to give five-membered metallacycles as exemplified by the reactions shown in Scheme 84.[138]

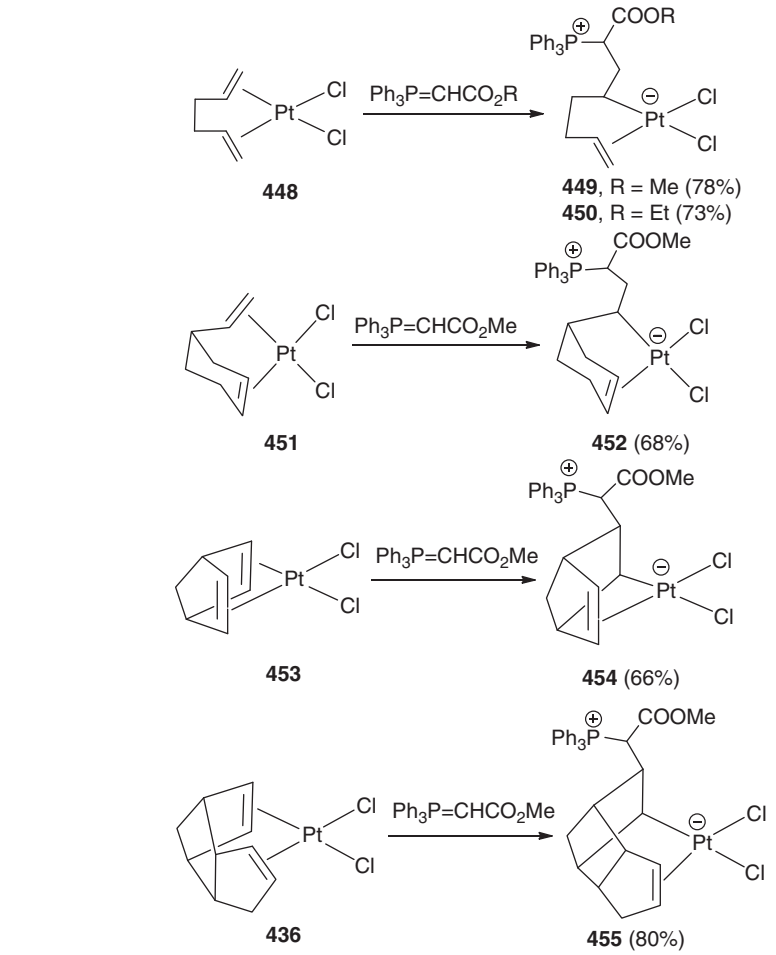
8-Vinylquinoline undergoes similar reactions. For example, treatment of $PdCl_2(PhCN)_2$ with 8-vinylquinoline and α-methyl-8-vinylquinoline followed by sodium dimethylmalonate produced the five-membered metallacycles **462** and **463**, respectively, as a result of selective nucleophilic addition of dimethylmalonate at the terminal vinyl carbons (Scheme 85).[139]

Addition reactions of carbon-based nucleophiles with monoolefin complexes of Pd and Pt are also known. For example, the alkyl complex **465** was isolated from the reaction of the alkene complex **464** with acetylacetone in the presence of Na_2CO_3 (Scheme 86),[140] the alkyl complex **467** was obtained from the reaction of the alkene complex **466** with sodium 2,4-pentanedionate.[141]

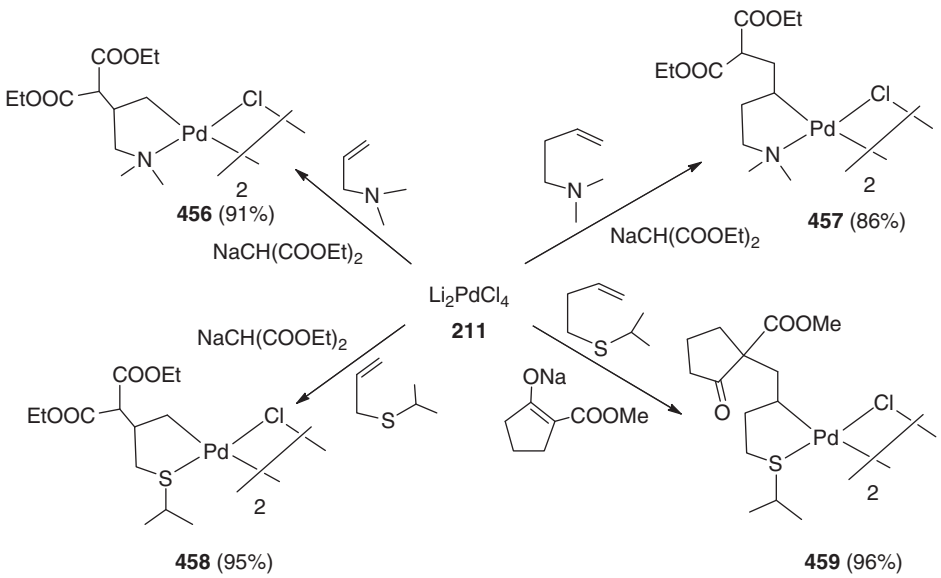
The platinum complexes $[PtCl(alkene)(tmeda)]ClO_4$ undergo addition reactions with stabilized carbon-based nucleophiles. They reacted with acidic carbon substrates such as acetylacetone, ethylacetoacetate, and diethylmalonate in the presence of Na_2CO_3 to give addition products.[142] For example, the alkene complex $[PtCl(CH_2{=}CH_2)(tmeda)]ClO_4$ (**468**) reacted with acetylacetone in the presence of Na_2CO_3 to give the alkyl complex **469** (Scheme 87). Reactions of substituted alkene complexes $[PtCl(alkene)(tmeda)]ClO_4$ with acetylacetonate anion have also been reported.[143] In general, the reactions produce a mixture of Markovnikov and *anti*-Markovnikov addition products with the Markovnikov adducts as the dominant products as illustrated by the reactions of the alkene complexes $[PtCl(CH_2{=}CHR)(tmeda)]ClO_4$ (**472**, R=Me; **473**, R=Ph) shown in Scheme 87.

Platinum complexes of the type $[PtCl(alkene)(tmeda)]ClO_4$ also undergo addition reactions with less common carbon-based nucleophiles. For example, *N*-methylaniline[144] and proton sponge[145] act as a carbon-based nucleophile to attack the olefin ligand of the alkene complex $[PtCl(CH_2{=}CH_2)(tmeda)]ClO_4$ (**468**) to give the alkyl complexes **478** and **479**, respectively (Scheme 88). The phosphorus ylide $Ph_3P{=}CHCOOMe$ reacted with the alkene complex **468** to give the alkyl complex **480**.

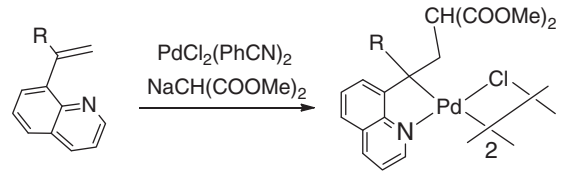
The dicationic ethylene complex $[Pt(CH_2{=}CH_2)(PNP)]ClO_4$ (**481**, PNP=2,6-$(Ph_2PCH_2)_2C_5H_3N$) can react with moderately electron-rich alkenes to give coupling products. For example, the alkene complex **481** reacted with a stoichiometric amount of the tri-substituted olefin 2-methyl-2-butene in $CH_2Cl_2/MeNO_2$ solution (10/1) to give the alkene complex **482** in a nearly quantitative



Scheme 83



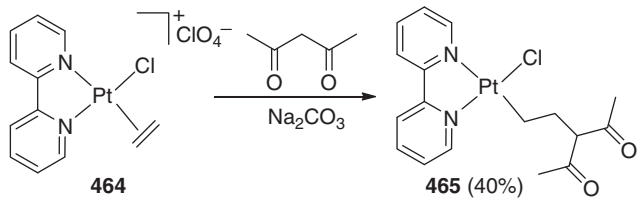
Scheme 84



460, R = H
461, R = Me

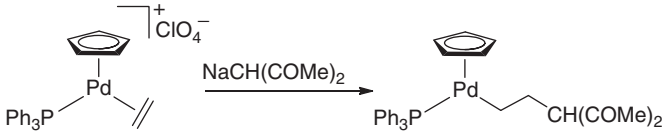
462, R = H (75%)
463, R = Me (83%)

Scheme 85



464

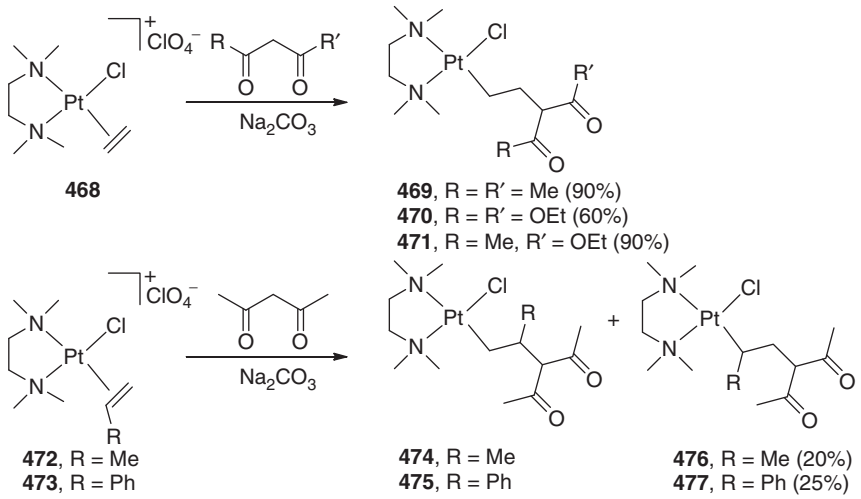
465 (40%)



466

467 (55%)

Scheme 86



468

469, R = R′ = Me (90%)
470, R = R′ = OEt (60%)
471, R = Me, R′ = OEt (90%)

472, R = Me
473, R = Ph

474, R = Me
475, R = Ph

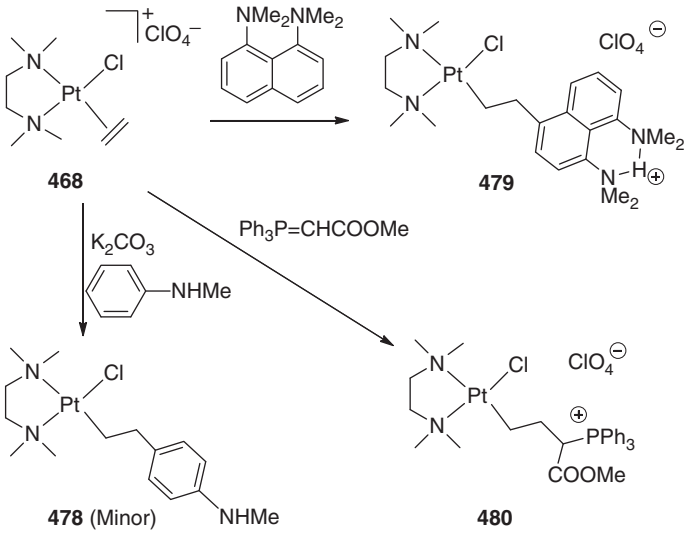
476, R = Me (20%)
477, R = Ph (25%)

Scheme 87

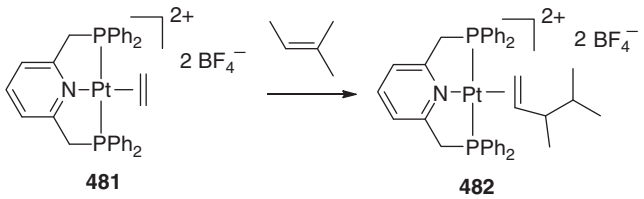
yield (Scheme 89). It was assumed that the reaction takes place via direct attack of 2-methyl-2-butene on the coordinated ethylene ligand which is activated by the doubly positive metal center.[146]

4.10.3.2 Reactions with Nitrogen-Based Nucleophiles

Attack of the amines on coordinated alkenes has often been suggested as one of the key step in catalytic hydroamination of alkenes.[147] Many stoichiometric reactions have been reported especially for alkene complexes of metals such as Mo, W, Fe, Rh, Pd, and Pt.



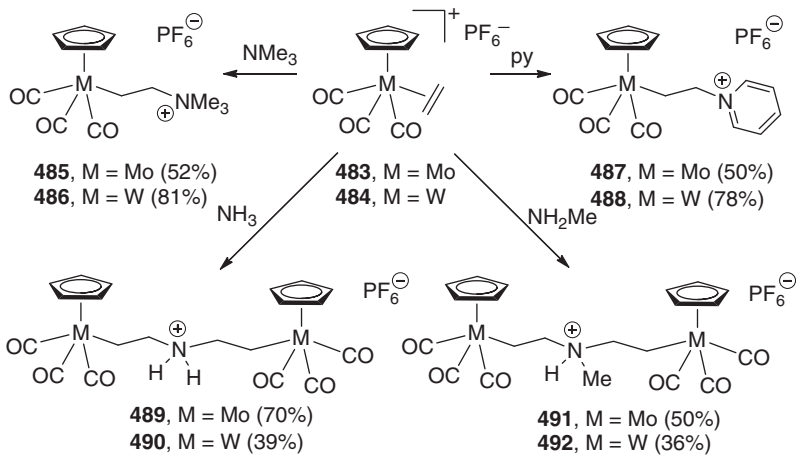
Scheme 88



Scheme 89

4.10.3.2.1 Reactions of group 6 metal complexes

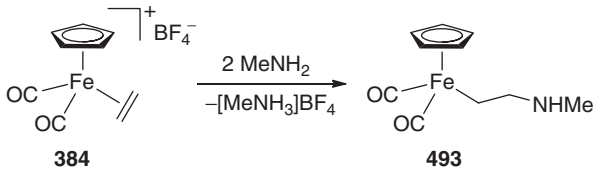
Addition of amines to alkenes coordinated to group 6 metals have been demonstrated with the metal complexes [CpM(CH_2═CH_2)$(CO)_3$]PF_6 (**483**, M=Mo; **484**, M=W).[148] For example, the alkene complexes [CpM(CH_2═CH_2)$(CO)_3$]PF_6 (**483**, M=Mo; **484**, M=W) reacted with NEt_3 and pyridine (py) to produce [CpM($CH_2CH_2NEt_3$)$(CO)_3$]PF_6 (**485**, M=Mo; **486**, M=W) and [CpM(CH_2CH_2py)$(CO)_3$]PF_6 (**487**, M=Mo; **488**, M=W), respectively (Scheme 90). Reactions of [CpM(CH_2═CH_2)$(CO)_3$]PF_6 (**483**, M=Mo; **484**, M=W) with NH_3 and NH_2Me produced the bimetallic complexes **489**–**490**, and **491**–**492**, respectively, because of bisalkylation of the amines.



Scheme 90

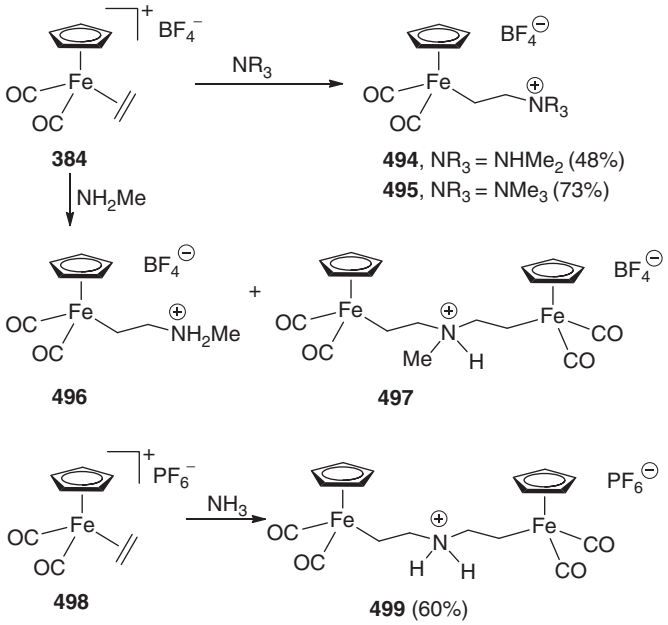
4.10.3.2.2 Reactions of group 8 metal complexes

Addition of amines to alkenes coordinated to group 8 metals have been demonstrated with metal complexes of the type [CpFe(alkene)$(CO)_2$]BF_4. Busetto et al. showed that the iron complex [CpFe($CH_2{=}CH_2$)$(CO)_2$]BF_4 (**384**) reacted with excess $MeNH_2$ to give the neutral alkyl complex **493** (Scheme 91).[149]



Scheme 91

Rosenblum and coworkers reexamined the reaction of [CpFe($CH_2{=}CH_2$)$(CO)_2$]BF_4 (**384**) with NH_2Me. They found that the reaction gave a mixture of the monoalkylated complex **496** and the bisalkylated complex **497**, with the bisalkylated product **497** as the major product (Scheme 92). The complex [CpFe($CH_2{=}CH_2$)$(CO)_2$]BF_4 (**384**) reacted with secondary and tertiary amines to



Scheme 92

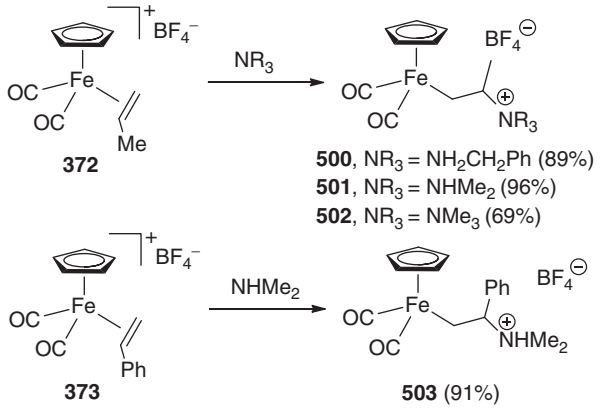
give monoalkylated products.[150] In a related study, Knoth found that the alkene complex [CpFe($CH_2{=}CH_2$)$(CO)_2$]PF_6 (**498**) reacted with NH_3 to give the bimetallic complex **499** (Scheme 92), and with pyridine (py) to give the alkyl complex [CpFe(CH_2CH_2py)$(CO)_2$]PF_6.[148]

The regioselectivity of reactions of [CpFe($CH_2{=}CHR$)$(CO)_2$]BF_4 with amines was found to be dependent on the substituents of the alkenes.[150,151] Treatment of the alkene complex [CpFe($CH_2{=}CHMe$)$(CO)_2$]BF_4 (**372**) with amines (am) such as $PhCH_2NH_2$, $NHMe_2$, and NEt_3 produced the alkyl complexes [CpFe(CH_2CHMe(am))$(CO)_2$]BF_4 (**500**, am = $PhCH_2NH_2$; **501**, am = $NHMe_2$, **502**, am = NEt_3) as a result of regiospecific addition of amines to the methyl-substituted olefinic carbon (Scheme 93). In contrast, treatment of the styrene complex [CpFe($CH_2{=}CHPh$)$(CO)_2$]BF_4 (**373**) with $NHMe_2$ produced the alkyl complex [CpFe($PhCHCH_2NHMe_2$)$(CO)_2$]BF_4 (**503**) as a result of regiospecific addition of the amine to the terminal olefinic carbon. The ammonium salts generated from the reactions can be used to prepare β-lactams.[151]

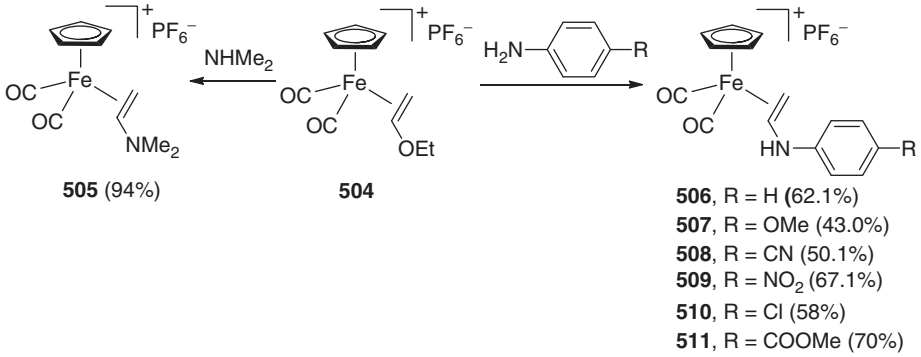
The vinylether complex [CpFe($CH_2{=}CHOEt$)$(CO)_2$]PF_6 (**504**) undergoes regioselective nucleophilic-substitution reactions with amines. For example, the complex **504** reacted with Me_2NH to give the alkyl complex **505**,[152,153] and with *para*-substituted anilines to give of η^2-vinyl aniline complexes (e.g., **506–511**) (Scheme 94).[154,155]

4.10.3.2.3 Reactions of group 9 metal complexes

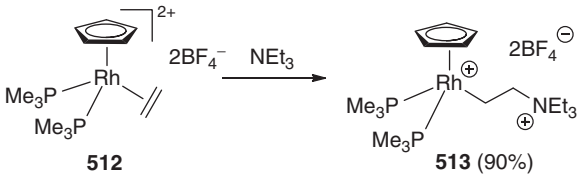
Addition of amines to alkenes coordinated to group 9 metals have been demonstrated with the metal complex [(η^6-C_6H_6)Rh($CH_2{=}CH_2$)$(PMe_3)_2$]$(BF_4)_2$ (**512**). The complex reacted with NEt_3 to give the alkyl complex **513** (Scheme 95).[156,157]



Scheme 93



Scheme 94



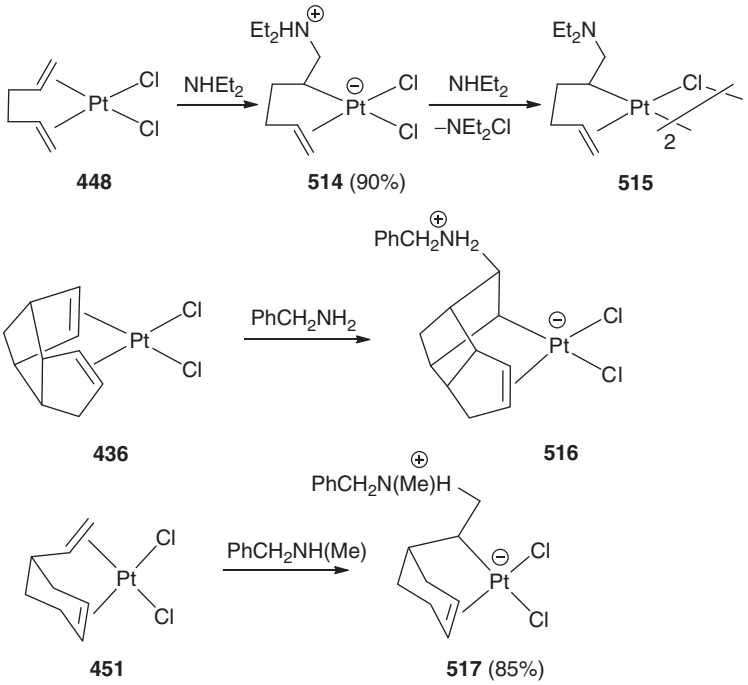
Scheme 95

4.10.3.2.4 Reactions of group 10 metal complexes

Nucleophile addition reactions of amines to alkenes coordinated to group 10 metals have been extensively investigated. The diene complexes MCl_2(dienes) (e.g. M = Pt, Pd; diene = cyclooctadiene, norbornadiene (NBD), dicyclopentadiene, 1,5-hexadiene, and 4-vinylcyclohexene) are known to readily react with ammonia, and aliphatic primary and secondary amines to give derivatives containing metal-carbon σ-bonds.[134,158–160] For example, the 1,5-hexadiene platinum complex **448** reacted with $NHEt_2$ to give the ionic enyl complex **514**, which can react further with $NHEt_2$ to give the neutral bimetallic enyl complex **515** (Scheme 96). The dicyclopentadiene complex **436** and the 4-vinylhexene complex **451** reacted with benzylamine to produce the enyl complexes **516** and **517**, respectively.

Kinetic and spectroscopic studies of the reactions of cyclohexylamine with the COD complexes MX_2(COD) (M = Pt, Pd; X = Cl, Br) in acetone (Scheme 97) reveal that the Pd complexes are more reactive than the Pt analogs and that MBr_2(1,5-COD) are more reactive than MCl_2(1,5-COD).[161]

Reactions of *trans*-PtX_2(alkene)(amine) (amine = NH_3, pyridine, amine; X = Cl, Br) with amines could lead to the formation of zwitterionic alkyl complexes.[162–168] For example, the amine complexes **524** and **525** reacted respectively with pyridine and 4-methylpyridine to give the zwitterionic alkyl complexes **526** and **527**; the amine complexes **528** and **530** reacted respectively with 3,5-dimethylpyridine and $NHEt_2$ to give the zwitterionic alkyl complexes **529** and **531** (Scheme 98).

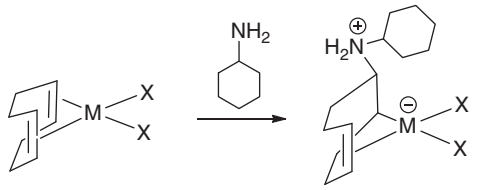


448 **514** (90%) **515**

436 **516**

451 **517** (85%)

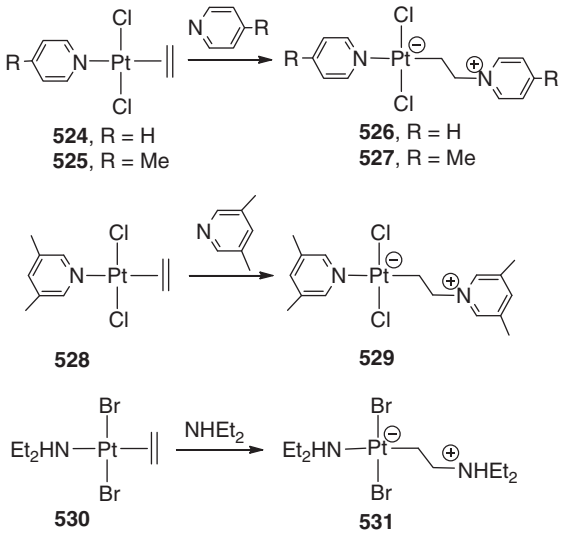
Scheme 96



430, M = Pd; X = Cl
431, M = Pt; X = Cl
518, M = Pd; X = Br
519, M = Pt; X = Br

520, M = Pd; X = Cl
521, M = Pt; X = Cl
522, M = Pd; X = Br
523, M = Pt; X = Br

Scheme 97



524, R = H
525, R = Me

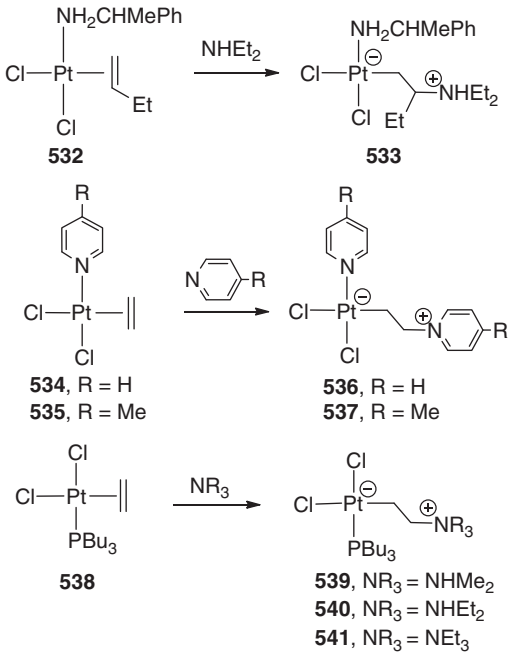
526, R = H
527, R = Me

528 **529**

530 **531**

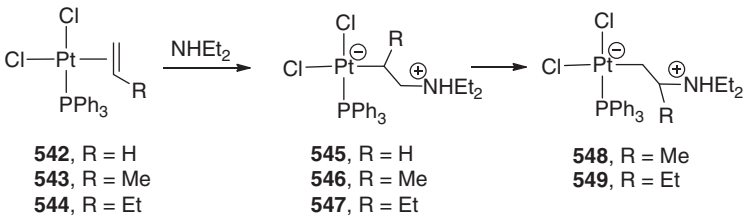
Scheme 98

Reactions of *cis*-$PtCl_2$(alkene)(L) (L = amine, pyridines, phosphines, DMSO) with amines to give zwitterionic alkyl complexes are also known. For example, the amine complex **532** reacted with $NHEt_2$ to give the zwitterionic alkyl complex **533**;[169] the pyridine complexes **534–535** reacted with pyridines to give the corresponding zwitterionic alkyl complexes **536–537** (Scheme 99).[170] The phosphine complex *cis*-$PtCl_2(CH_2{=}CH_2)(PBu_3)$ (**538**) reacted with $NHMe_2$, $NHEt_2$, and NEt_3 to give the zwitterionic alkyl complexes **539**, **540**, and **541**, respectively.[171]



Scheme 99

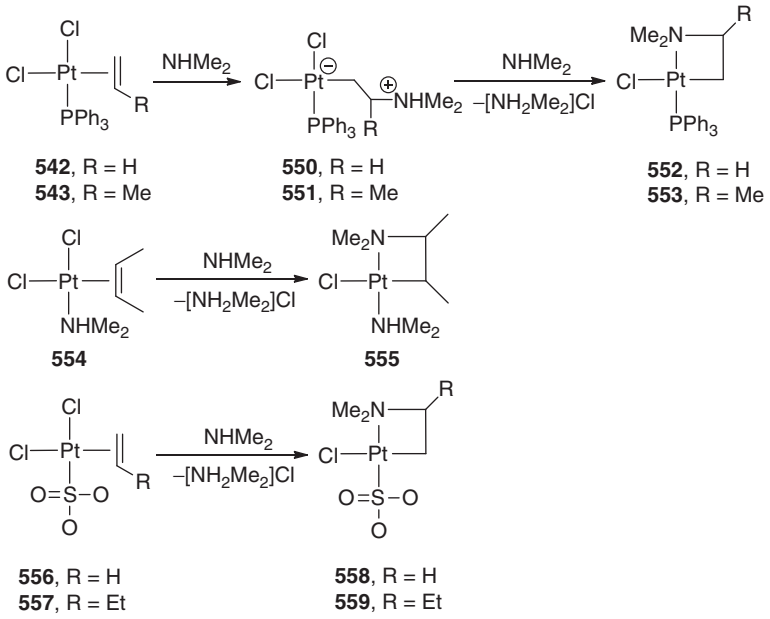
In most of the reported amine addition reactions involving unsymmetrically substituted alkenes, the isolated products are Markovnikov addition products formed by attack of the amines on more substituted olefinic carbons. Recently, Atwood and coworkers reexamined the amination reactions of the alkene complexes $PtCl_2$(alkene)(PPh_3) (alkene = ethylene, propene, 1-butene). They found that the reactions of $PtCl_2$(alkene)(PPh_3) (**543**, alkene = propene, **544**, alkene = 1-butene) with $NHEt_2$ at low-temperature lead to the *anti*-Markovnikov nucleophilic addition products (**546** and **547**), which slowly isomerize at room temperature to give the Markovnikov products (**548** and **549**) (Scheme 100).[172]



Scheme 100

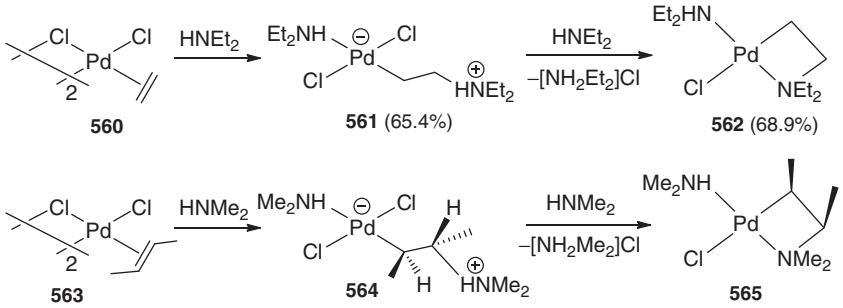
When excess amines are used, the zwitterionic alkyl complexes formed from initial reactions of $PtCl_2$(alkene)(L) could be deprotonated to give chelating β-aminoalkyl platinum complexes. For example, the alkene complex $PtCl_2(CH_2{=}CH_2)(PPh_3)$ (**542**) reacted with excess $NHMe_2$ to give first the zwitterionic alkyl complex **550** and then the metallacyclic complex **552**,[173–176] the alkene complexes **554** and **556** reacted with excess $NHMe_2$ to produce the chelating β-aminoalkyl complexes **555** and **558**, respectively (Scheme 101).[177–179]

Reactions of $[PdCl_2$(alkene)$]_2$ with amines give similar results. The reactions usually give initially a zwitterionic complex, which can react further with additional amine to give a chelating β-aminoalkylpalladium complex.[180,181] For example, the alkene complex $[PdCl_2(CH_2{=}CH_2)]_2$ (**560**) reacted with $NHEt_2$ to give the zwitterionic complex **561**, and then the β-aminoalkylpalladium complex **562**; the alkene complex $[PdCl_2((E)$-CHMe=CHMe$)]_2$ (**563**) reacted similarly with $NHMe_2$ to give the



Scheme 101

zwitterionic alkyl complex **564**, and then the chelating *β*-aminoalkyl palladium complex **565** in which the two methyl groups are *cis* to each other (Scheme 102).



Scheme 102

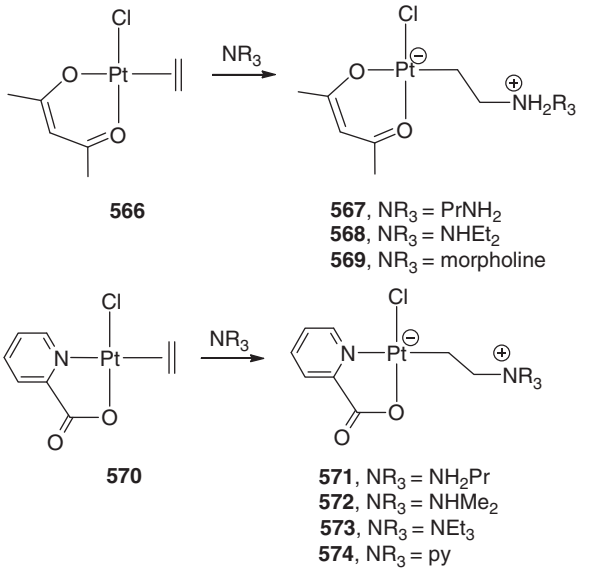
Platinum alkene complexes with an anionic bidentate ligand can also undergo nucleophilic addition reactions with amines. For example, the platinum alkene complexes **566** and **570** reacted with a variety of amines to produce the corresponding zwitterionic complexes (Scheme 103).[182,183]

The platinum ethylene complex (PyPyr)PtCl(C_2H_4) (**575**) reacted with one equivalent of LiN*i*Pr_2, LiNH(*o*-xylyl) and LiN($SiMe_3$)$_2$ to produce the platinum complexes **582**, **583**, and **584**, respectively (Scheme 104). It was suggested the products were produced through intermediates **576–578** formed by direct nucleophilic attack of an amide on coordinated olefin.[184]

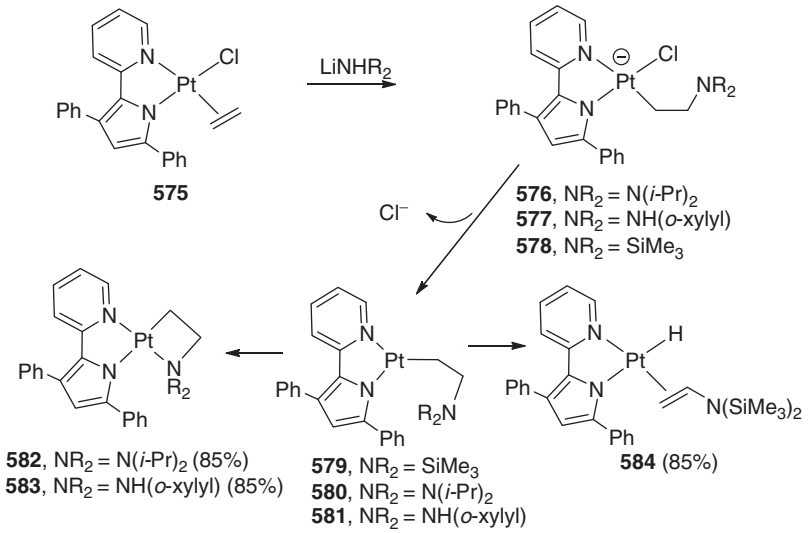
The cationic Pt complexes [PtCl(CH_2═CHR)(tmeda)]$^+$ (tmeda═*N*,*N*,*N*,*N*-tetramethylethylenediamine) are reactive toward various nitrogen-based nucleophiles.[185] The alkene complex [PtCl(CH_2═CH_2)(tmeda)]ClO_4 (**468**) reacted with N_3^- and NO_2^- to give **585** and **586**, respectively (Scheme 105). The complex **468** also reacted with sodium cyanate to afford the metallacyclic complex **588**, which was formed by initially nucleophilic attack of a cyanate ion to form the intermediate **587**, followed by coordination of a second cyanate ion and protonation.[186,187]

The ethylene complex [PtCl(CH_2═CH_2)(tmeda)]ClO_4 (**468**) reacted with *N*-methylaniline to give the cationic alkyl complex **589**, which can be deprotonated by K_2CO_3 to give the neutral alkyl complex **590** (Scheme 106).[144] The reaction of the ethylene complex [PtCl{CH_2═$CHCH_2OC(O)Me$}(tmeda)]ClO_4 (**591**) with primary amines lead to substitution of the acetate group and addition of the amines to the olefinic double bond to give a mixture of alkyl complexes (Scheme 106).[188]

Monometallic, bimetallic, and trimetallic complexes have been isolated from the reactions of $NHEt_2$ with the ethylene complex [PtCl(CH_2═CH_2)(tmeda)]ClO_4 (**468**) depending on the relative amount of the reagents (Scheme 107).[189] The tetrametallic complex **599** was isolated from the reaction of the ethylene complex **468** with NH_3.



Scheme 103

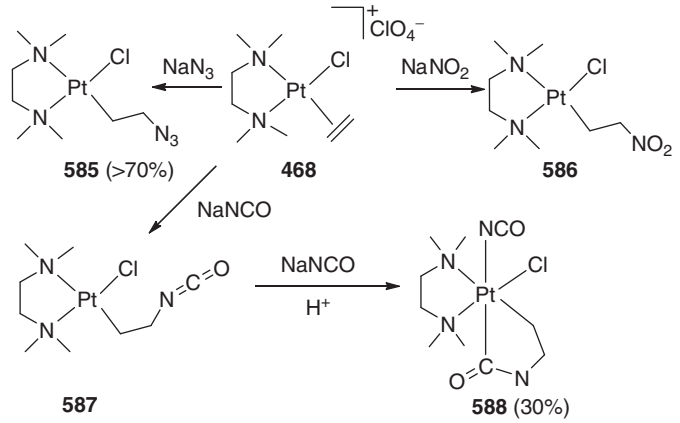


Scheme 104

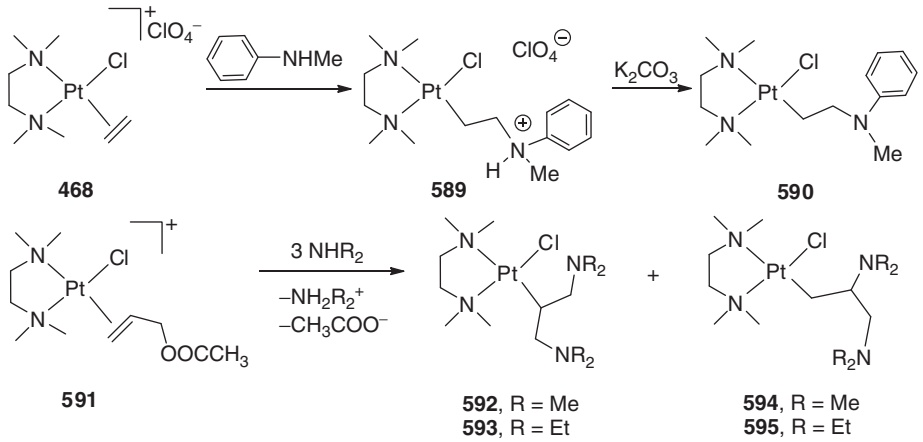
Reactions of mono-substituted alkene complexes $[PtCl(CH_2{=}CHR)(tmeda)]ClO_4$ with secondary amines such as $NHMe_2$ and $NHEt_2$ were found to produce a mixture of Markovnikov and *anti*-Markovnikov addition products, which in basic medium undergo an intramolecular nucleophilic-substitution reaction with the elimination of the chlorido ligand to form an azaplatinacyclobutane complex (Scheme 108).[190,191] Kinetic study shows that the Markovnikov isomer is kinetically favored in the amination reactions and isomerization from the Markovnikov to the *anti*-Markovnikov addition products takes place readily at room temperature. It was noted that a deprotonation reaction may occur when the complexes $[PtCl(CH_2{=}CHR)(tmeda)]ClO_4$ were treated with bulky amines. For example, the reaction of $[PtCl(CH_2{=}CHPh)(tmeda)]ClO_4$ with triethylamine leads to the abstraction of a vinylic proton to form the alkenyl platinum complex $PtCl(CH{=}CHPh)(tmeda)$.[192]

Like $[PtCl(alkene)(tmeda)]ClO_4$, the complexes $[PtCl(alkene)(bipy)]ClO_4$ also undergo similar amination reactions. For example, the complex $[PtCl(CH_2{=}CH_2)(bipy)]ClO_4$ (**464**) reacted with NEt_3 to give the alkyl complex **616**, and with $NHEt_2$ to give the alkyl complex **617**, which can be converted into the metallacyclic complex **618** on further reaction with $NHEt_2$ (Scheme 109).[140]

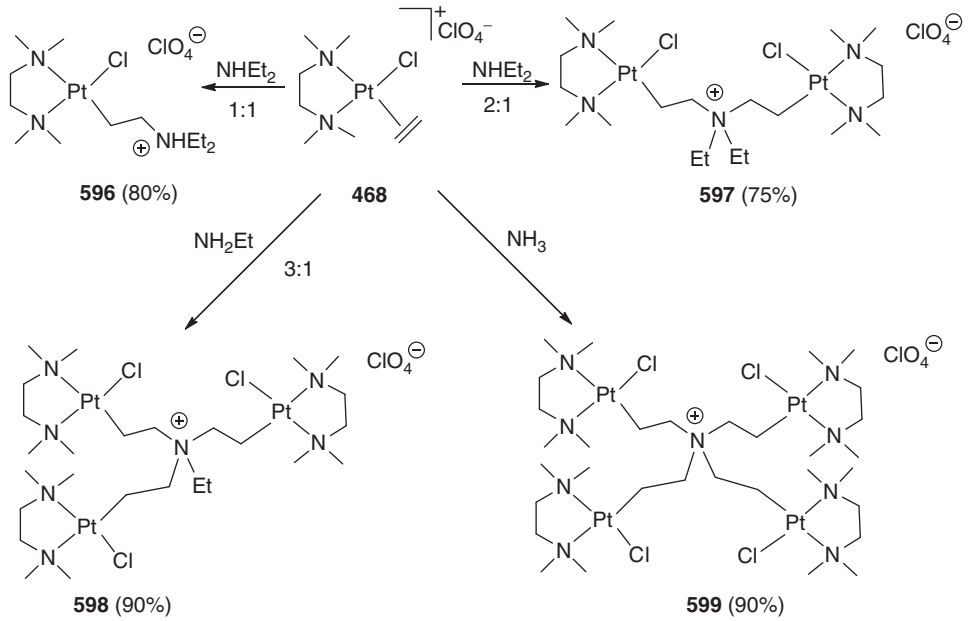
The dicationic palladium alkene complexes $[Pd(alkene)(PNP)](BF_4)_2$ (alkene = ethylene, propene, styrene; PNP = 2,6-$(Ph_2PCH_2)_2C_5H_3N$)) undergo nucleophilic addition reactions with secondary amines and aromatic amines.[193,194] For example, the ethylene complex $[Pd(CH_2{=}CH_2)(PNP)](BF_4)_2$ (**619**) reacted with excess piperidine to give the alkyl complex **620**; the



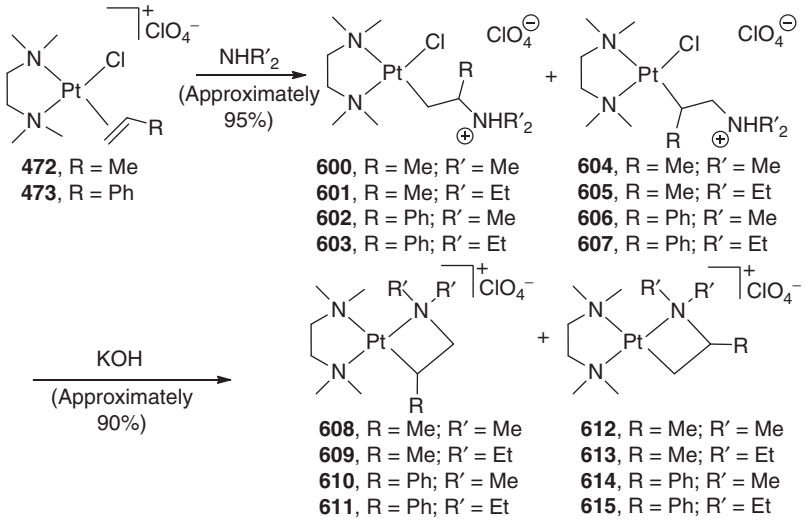
Scheme 105



Scheme 106



Scheme 107



472, R = Me
473, R = Ph

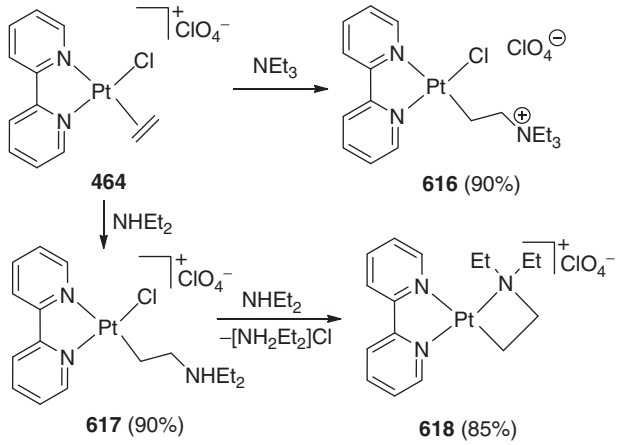
600, R = Me; R′ = Me
601, R = Me; R′ = Et
602, R = Ph; R′ = Me
603, R = Ph; R′ = Et

604, R = Me; R′ = Me
605, R = Me; R′ = Et
606, R = Ph; R′ = Me
607, R = Ph; R′ = Et

608, R = Me; R′ = Me
609, R = Me; R′ = Et
610, R = Ph; R′ = Me
611, R = Ph; R′ = Et

612, R = Me; R′ = Me
613, R = Me; R′ = Et
614, R = Ph; R′ = Me
615, R = Ph; R′ = Et

Scheme 108



464

616 (90%)

617 (90%)

618 (85%)

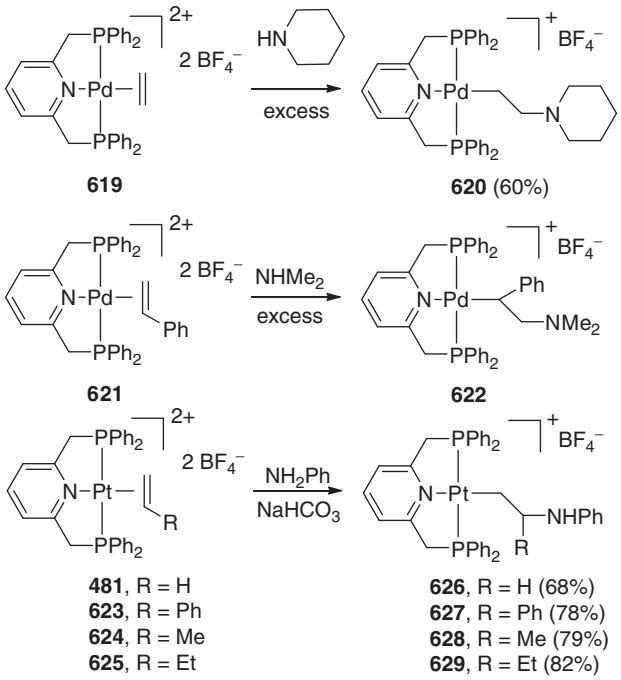
Scheme 109

styrene complex $[Pd(CH_2{=}CHPh)(PNP)](BF_4)_2$ (**621**) reacted with excess $HNMe_2$ to give the alkyl complex **622** (Scheme 110). The platinum complexes of the type $[Pt(alkene)(PNP)](BF_4)_2$ undergo similar amination reactions.[195] For example, the complexes $[Pt(alkene)(PNP)](BF_4)_2$ (**481**, alkene$=CH_2{=}CH_2$; **623**, alkene$=CH_2{=}CHPh$) reacted regioselectively with aniline in the presence of $NaHCO_3$ to give the alkyl complexes $[Pt(CH_2CHRNHPh)(PNP)](BF_4)_2$ (**626**, R$=$H; **627**, R$=$Ph).

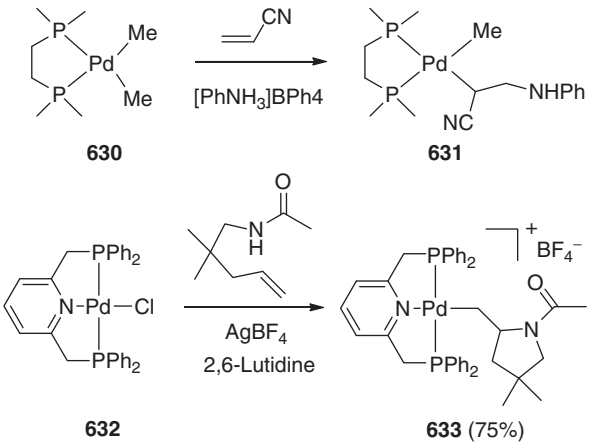
Amination reactions also occurred in the reactions of $PdMe_2(dmpe)$ (dmpe$=Me_2PCH_2CH_2PMe_2$) with acrylonitrile and $[PhNH_3]BPh_4$ and in the reaction of aminoalkenes with (PNP)PdCl/$AgBF_4$ (PNP$=$2,6-$(Ph_2PCH_2)_2C_5H_3N$)). Treatment of $PdMe_2(dmpe)$ (**630**) with excess acrylonitrile and $[PhNH_3]BPh_4$ produced the alkyl complex **631** (Scheme 111).[196] The reaction presumably proceeded through initial formation of the intermediate $[PdMe(CH_2{=}CHCN)(dmpe)]BPh_4$ followed by nucleophilic attack of $PhNH_2$ on the coordinated alkenes. The reaction of the aminoalkene *N*-(2,2-dimethylpentyl)acetamide with PdCl(PNP) (**632**), $AgBF_4$, and 2,6-lutidine in dichloromethane afforded the palladium alkyl complex **633** as a result of intramolecular amination reaction.[197]

4.10.3.3 Reactions with Oxygen-Based Nucleophiles

Attack of hydroxide and alkoxy group on coordinated alkenes has often been suggested as one of the key steps in catalytic hydroalkoxylation[198] and hydration[199] of alkenes, and Wacker oxidation and related processes.[200] Many stoichiometric reactions have also been reported especially for alkene complexes of group 8–10 metals.



Scheme 110



Scheme 111

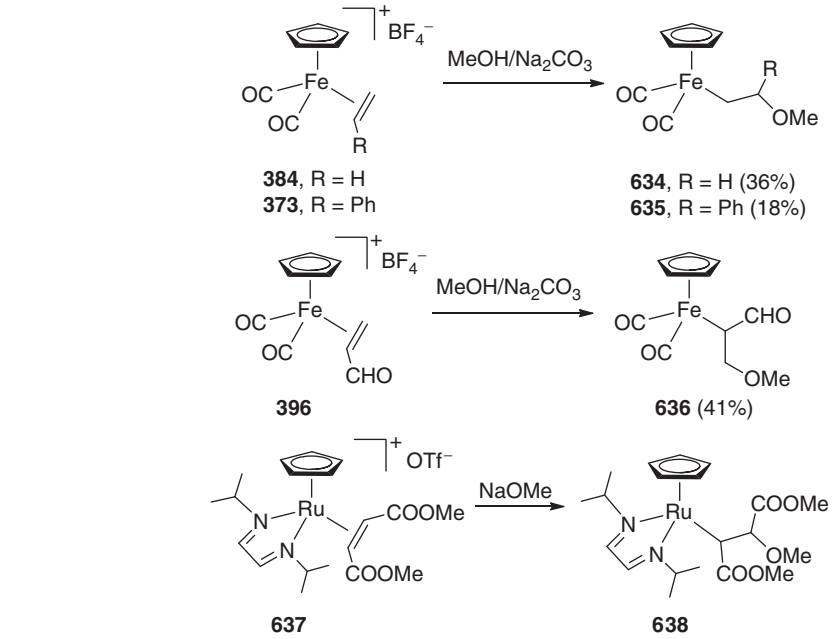
4.10.3.3.1 Reactions of group 8 metal complexes

Nucleophilic addition of alkoxides to alkenes coordinated to group 8 metals has been reported for complexes of iron and ruthenium. Iron complexes $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ react with alcohols R′OH in the presence of Na_2CO_3 to produce the alkyl complexes $CpFe\{CH_2CHR(OR')\}(CO)_2$.[149,150] For example, treatment of $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ (**384**, R=H; **373**, R=Ph) and $[CpFe(CH_2{=}CHCHO)(CO)_2]BF_4$ (**396**) with methanol in the presence of Na_2CO_3 produced the alkyl complexes **634**, **635**, and **636**, respectively (Scheme 112). The ruthenium complex **637** reacted with NaOMe to produce the alkyl complex **638**.[55]

Reactions of the alkene complexes $CpFe(CO)_2(CH_2{=}CHCH_2CRR'OBF_3)$ (**639–643**) with KO*t*Bu in CH_2Cl_2 afforded the corresponding iron alkyl complexes **644–648,** which can be converted into the furan esters **649–653** on treatment with ceric ammonium nitrate under an atmosphere of CO (Scheme 113). The chemistry has been used for the synthesis of furan and pyrrolidine derivatives.[201–203]

4.10.3.3.2 Reactions of group 9 metal complexes

Several examples of nucleophilic attack of alkoxides of alkenes coordinated to group 9 metals have been reported. The bromo (pyridine)cobaloxime **654** reacted with ethyl vinylether in ethanol in the presence of triethylamine to give a mixture of



384, R = H
373, R = Ph

634, R = H (36%)
635, R = Ph (18%)

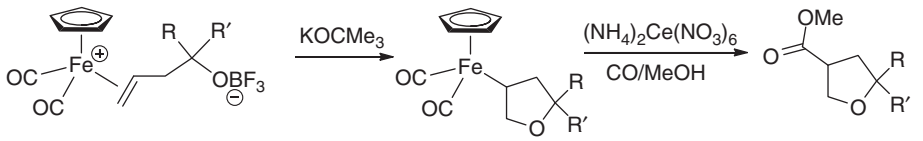
396

636 (41%)

637

638

Scheme 112



639, R = H, R′ = Ph
640, R = H, R′ = *m*-PhNO$_2$
641, R = H, R′ = *m*-PhOMe
642, R = Me, R′ = Ph
643, R = R′ = *c*-C$_6$H$_{11}$

644, R = H, R′ = Ph (80%)
645, R = H, R′ = *m*-PhNO$_2$ (80%)
646, R = H, R′ = *m*-PhOMe (75%)
647, R = Me, R′ = Ph (50%)
648, R = R′= *c*-C$_6$H$_{11}$ (45%)

649, R = H, R′ = Ph (45%)
650, R = H, R′ = *m*-PhNO$_2$ (43%)
651, R = H, R′ = *m*-PhOMe (45%)
652, R = Me, R′ = Ph (20%)
653, R = R′ = *c*-C$_6$H$_{11}$ (19%)

Scheme 113

2,2-diethoxyethyl(pyridine)cobaloxime (**665**) and formylmethyl(pyridine)cobaloxime (**656**), through attack of EtOH on the coordinated vinylether of the intermediate **655** (Scheme 114).[204] The reaction is relevant to the action of vitamin B_{12} coenzymes in their catalyzed-rearrangement reactions.[205]

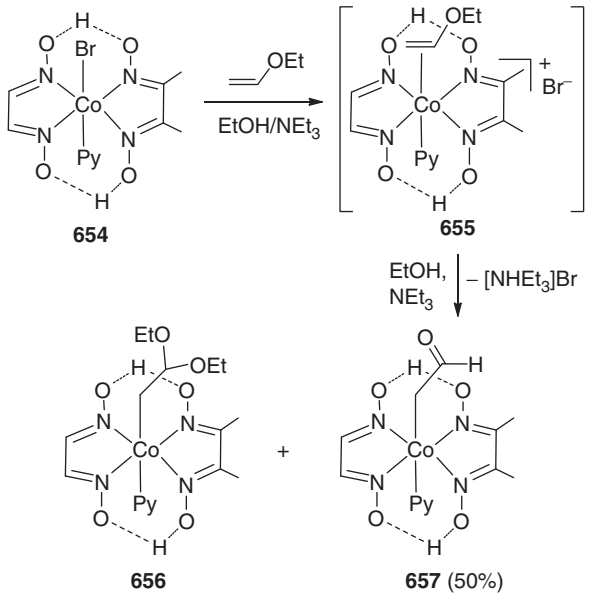
Diene ligands coordinated to group 9 metals can be attacked by alkoxides. For example, the diene iridium complex **658** reacted with NaOMe to yield the 8-methoxycycloocta-4-enyl complex **659** (Scheme 115);[206] the iridium complex [Ir(tripod)(COD)]Cl (**660**, tripod = MeC(CH$_2$PPh$_2$)$_3$) reacted with alkoxides (MeO$^-$, EtO$^-$, *i*PrO$^-$) to give the corresponding 2-alkoxycyclooct-5-en-1-yl iridium complexes **661–663** (Scheme 115).[207] A similar reaction occurred between alkoxides (MeO$^-$, *i*PrO$^-$, *t*BuO$^-$, and 2-BuO$^-$) and the rhodium complex [Rh(tripod)(NBD)]Cl (**664**, NBD = norbornadiene) to give the 2-alkoxynorborn-4-en-1-yl rhodium complexes **665–668**.

As a rare example of addition of oxygen-based nucleophiles to well-defined monoolefin complexes of group 9 metals, the rhodium complex [(η^6-C$_6$H$_6$)Rh(CH$_2$=CH$_2$)(PMe$_3$)$_2$](BF$_4$)$_2$ (**512**) reacted with NaOMe to give the alkyl complex **669** (Scheme 116).[156,157]

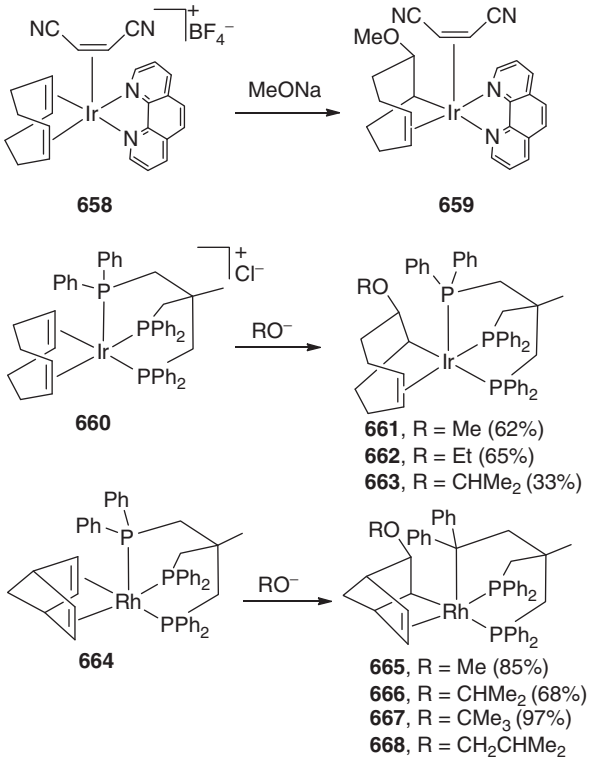
4.10.3.3.3 Reactions of group 10 metal complexes

Many examples of nucleophilic addition reactions of oxygen-based nucleophiles with group 10 metal alkene complexes have been documented. Diene complexes of the general type MCl$_2$(dienes) (M = Pt, Pd, diene = cyclooctadiene, NBD, dicyclopentadiene, 1,5-hexadiene, and 4-vinylcyclohexene) are known to reacted with RONa or ROH/Na$_2$CO$_3$[208–211] to give derivatives containing metal–carbon σ-bonds. The addition reactions also occurred in the direct reactions of dienes with chloroplatinate or palladate in alcohols. Some examples are shown in Scheme 117.

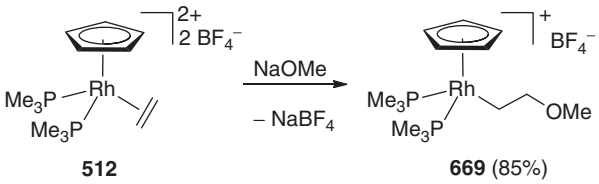
As additional examples of nucleophilic attack of alkoxides on dienes coordinated to group 10 metals, 7-methylenebicyclo [2.2.1]hep-2-ene derivatives **679** and **680** reacted with PdCl$_2$(PhCN)$_2$ in nonpolar solvents such as CHCl$_3$ and CH$_2$Cl$_2$ to give the enyl complexes **681** and **682** (Scheme 118).[212]



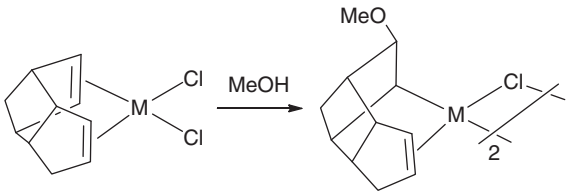
Scheme 114



Scheme 115

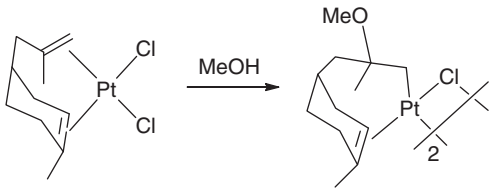


Scheme 116



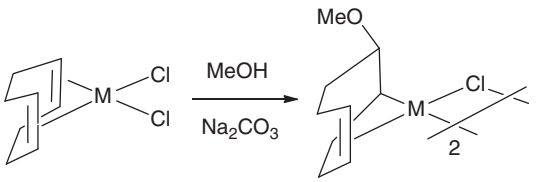
436, M = Pt
438, M = Pd

670, M = Pt (94.2%)
671, M = Pd (88.6%)



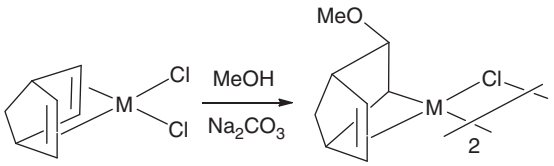
672

673 (2.7%)



430, M = Pd
431, M = Pt

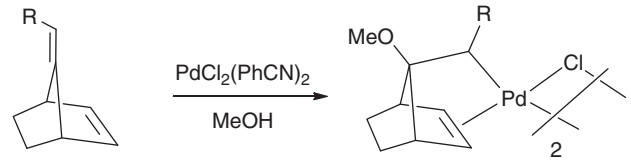
674, M = Pd (30%)
675, M = Pt (60.8%)



676, M = Pd
453, M = Pt

677, M = Pd (80%)
678, M = Pt (59%)

Scheme 117

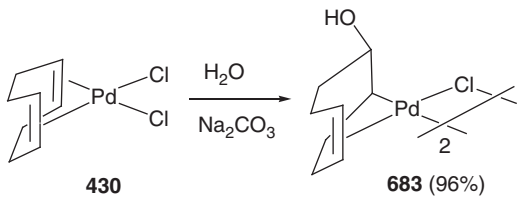


679, R = COOMe
680, R = COOEt

681, R = COOMe (87%)
682, R = COOEt (93%)

Scheme 118

Diene complexes of the type MCl_2(dienes) (M = Pt, Pd) could also react with water or hydroxide to give σ-bonded hydroxyl enyl complexes. For example, the palladium complex $PdCl_2$(COD) (**430**) reacted with water in the presence of Na_2CO_3 to produce the σ-bonded hydroxyl enyl complex **683** in which the OH group is *trans* to Pd (Scheme 119).[213,214]



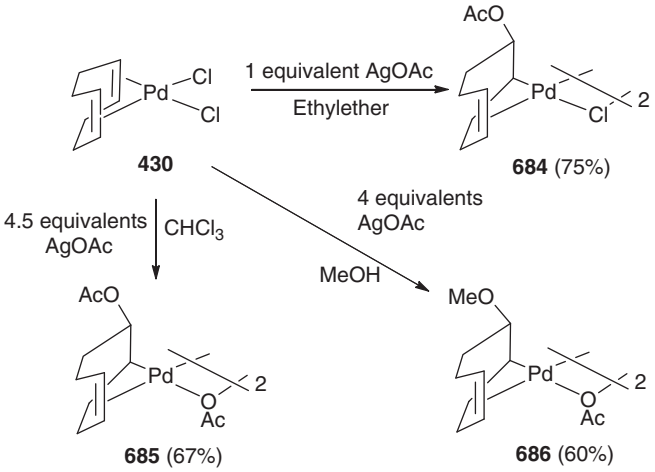
430

683 (96%)

Scheme 119

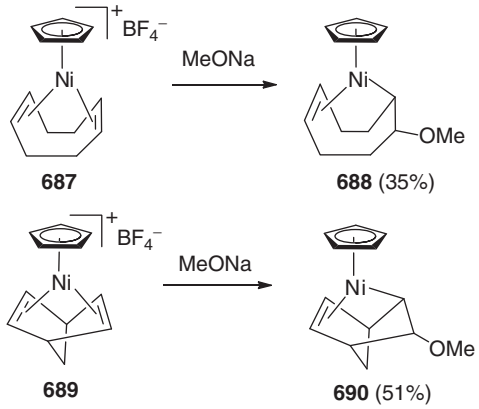
Similar addition reactions of OMe^- and OH^- were observed in the reactions of methanol[215] and water[216] with complexes of the type $[M(diene)(LL)_2](PF_6)_2$ (M = Pd, diene = 1,5-cyclooctadiene, *endo*-dicyclopentadiene, LL = 2,2′-bipyridyl, 1,10-phenanthroline; M = Pd, diene = dicyclopentadiene, LL = dppe; M = Pd, diene = 1,5-cyclooctadiene, LL = ethylenediamine; M = Pt, diene = 1,5-cyclooctadiene, LL = 2,2′-bipyridyl, 1,10-phenanthroline).

The diene ligands of complexes MCl_2(dienes) (M = Pt, Pd) could also be attacked by carboxylates.[217–219] For example, the 1.5-cyclooctadiene palladium complex **430** reacted with AgOAc to give enyl complexes **684**, **685**, or **686**, depending on the reaction conditions (Scheme 120).



Scheme 120

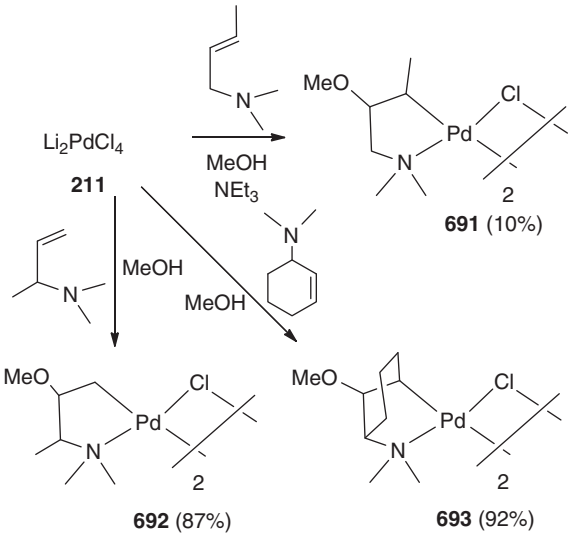
Although rare, nucleophilic attack of oxygen-based nucleophiles on dienes coordinated to nickel has also been reported. The nickel complexes [CpNi(COD)]BF_4 (**687**) and [CpNi(NBD)]BF_4 (**689**) reacted with MeONa to give the enyl complexes **688** and **690**, respectively (Scheme 121).[220]



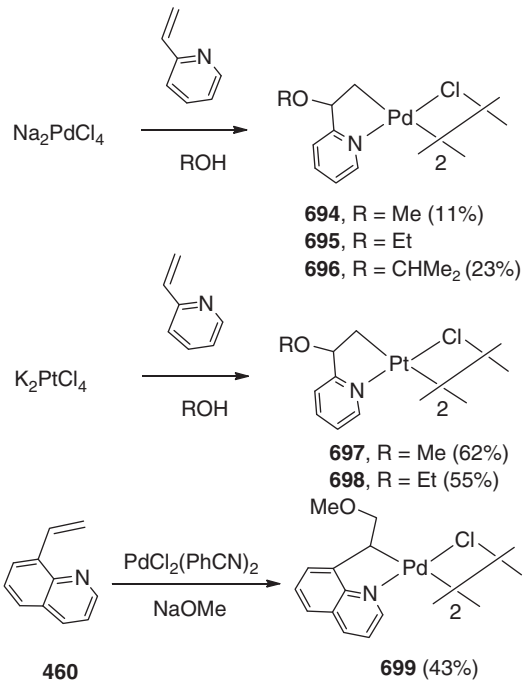
Scheme 121

Palladium complexes of hetero-substituted alkenes can undergo intermolecular nucleophilic addition reactions with alkoxides to give metallacycles. For example, dimethylamino-*trans*-2-butene reacted with Li_2PdCl_4 (**211**) in methanol in the presence of NEt_3 to give the bimetallic complex **691**,[221] racemic *N*,*N*-dimethylamino-3-but-1-ene and *N*,*N*-dimethylamino-1-cyclohex-2-ene reacted with Li_2PdCl_4 in methanol to produce the bimetallic complexes **692** and **693**, respectively (Scheme 122).[222,223]

2-Vinylpyridine and 8-vinylquinoline undergoes similar reactions. For example, the reactions of 2-vinylpyridine with Na_2PdCl_4 and K_2PtCl_4 in alcohols (ROH) produced the bimetallic complexes **694–696** and **697–698**, respectively (Scheme 123).[224] Treatment of $PdCl_2(PhCN)_2$ with 8-vinylquinoline followed by sodium methoxide produced the five-membered metallacyclic complex **699**.[139]



Scheme 122

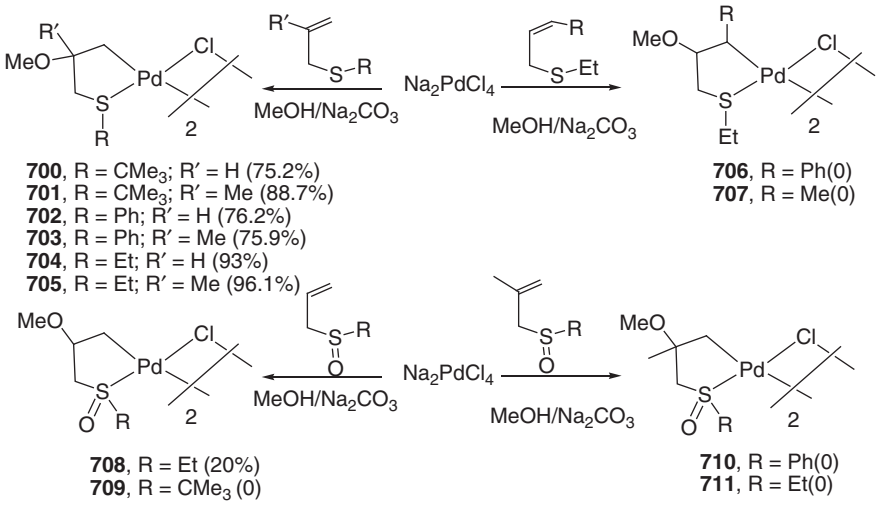


Scheme 123

Palladacycles can also be produced from the reactions of allylic sulfides or sulphoxides with palladium salts and alcohols. For example, terminal allylic sulfides reacted with Na_2PdCl_4 in methanol in the presence of Na_2CO_3 to produce bimetallic mercapto-2-methoxy propyl complexes (e.g., **700–705**); the reaction of the terminal allylic sulphoxide $CH_2{=}CHCH_2S(O)Et$ gave analogous bimetallic complex **708** (Scheme 124).[225] However, reactions of crotyl and cinnamyl sulfides with Na_2PdCl_4 did not give the analogous complexes (**706–707**). The expected products **709–711** were also not obtained in the reactions of Na_2PdCl_4 with $CH_2{=}CHCH_2S(O)CMe_3$ and $CH_2{=}CHCH_2S(O)R$ (R=Ph, Et).

Similarly, 1-(phenylthio)-2,4-pentadiene reacted with Na_2PdCl_4 in methanol in the presence of Na_2CO_3 to give the bimetallic complex **713** (Scheme 125).[226]

Several addition reactions of oxygen-based nucleophiles with monoolefin complexes of group 10 metals have been described in the literature. The alkene complex $[Pt(NO_2)(MeCH{=}CHR)(tmeda)]ClO_4$ (**714**, R=H; **715**, R=Me) underwent intramolecular attack of the nitro group on the *cis*-olefin ligand to give the metallacyclic complexes $[Pt\{(NO_2)MeCH{=}CHR\}(tmeda)]ClO_4$ (**716**,



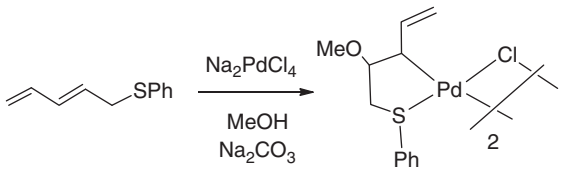
700, R = CMe_3; R′ = H (75.2%)
701, R = CMe_3; R′ = Me (88.7%)
702, R = Ph; R′ = H (76.2%)
703, R = Ph; R′ = Me (75.9%)
704, R = Et; R′ = H (93%)
705, R = Et; R′ = Me (96.1%)

706, R = Ph(0)
707, R = Me(0)

708, R = Et (20%)
709, R = CMe_3 (0)

710, R = Ph(0)
711, R = Et(0)

Scheme 124

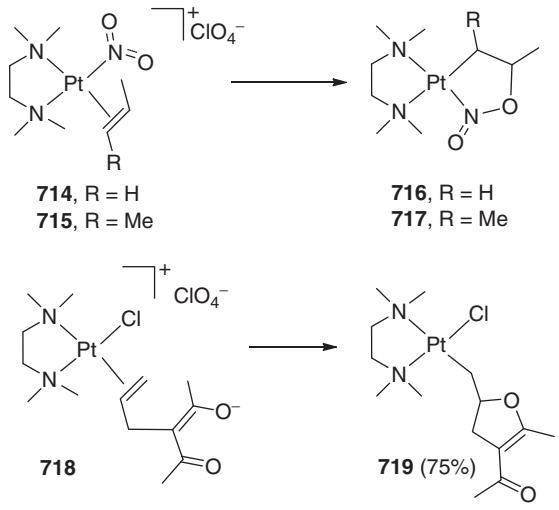


712

713 (59%)

Scheme 125

R=H; **717**, R=Me) (Scheme 126).[227] The alkene complex **718** undergoes an intramolecular nucleophilic addition reaction to give the alkyl complex **719**.[188]



714, R = H
715, R = Me

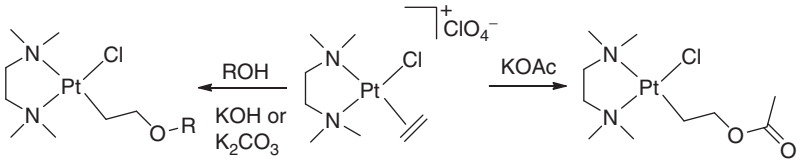
716, R = H
717, R = Me

718

719 (75%)

Scheme 126

Complexes of the type $[PtCl(alkene)(tmeda)]^+$ can also undergo intermolecular nucleophilic addition reactions with oxygen-based nucleophiles. For example, the ethylene complex $[PtCl(CH_2{=}CH_2)(tmeda)]ClO_4$ (**468**) reacted with water, alcohols, and phenol under basic condition to give alkyl complexes of the general formula $PtCl(CH_2CH_2OR)(tmeda)$ (**720–722**), and with KOAc to give the alkyl complex $PtCl(CH_2CH_2O_2CMe)(tmeda)$ (**723**) (Scheme 127).[144,228]



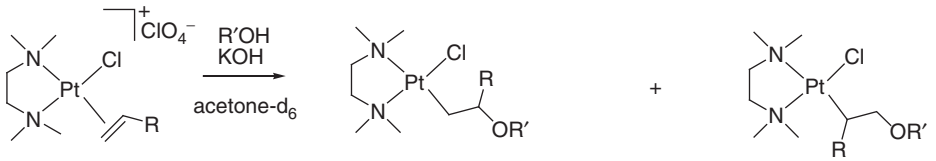
720, R = H (80%)
721, R = Et (85%)
722, R = Ph (95%)

468

723

Scheme 127

Addition reactions of substituted alkene complexes [PtCl(alkene)(tmede)]ClO_4 (alkene = propene, styrene, 2-butene) with OH^- or OR^- are also known. The reactions produce either the Markovnikov adduct only or a mixture of Markovnikov and *anti*-Markovnikov adducts, depending on the substituents on the alkenes, as illustrated by the relative amounts of the products determined by NMR shown in Scheme 128.[143,229]



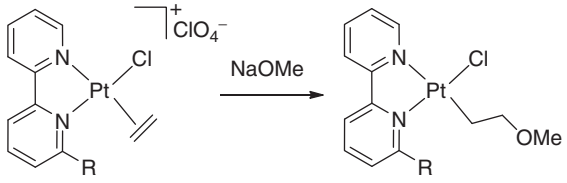
472, R = Me
473, R = Ph
724, R = 4-OMe-Ph
725, R = 4-CF_3-Ph

726, R = Me; R′ = H (100%)
727, R = Ph; R′ = H (100%)
728, R = 4-OMe-Ph; R′ = OMe (>90%)
729, R = 4-CF_3-Ph; R′ = OMe (30%)

730, R = 4-OMe-Ph; R′ =OMe (<10%)
731, R = 4-CF_3-Ph; R′ = OMe (70%)

Scheme 128

As expected, the bipryidine complexes [PtCl(alkene)(bipy)]$^+$ undergo similar addition reactions with alkoxides.[140,230–232] For example, the bipyridine complexes **464** and **732** reacted with NaOMe to produce the alkyl complexes **733** and **734**, respectively (Scheme 129).



464, R = H
732, R = Me

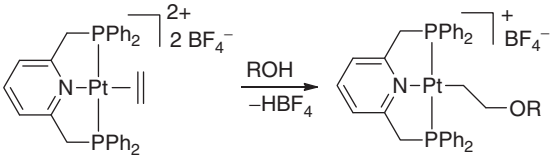
733, R = H (>95%)
734, R = Me (60%)

Scheme 129

It has also been demonstrated the alkene ligands in dicationic complexes [Pt(alkene)(PNP)]$^{2+}$ (M = Pt, Pd; PNP = 2,6-$(Ph_2PCH_2)_2C_5H_3N$) can be attacked by water and alcohols. For example, the platinum complex [Pt(CH_2=CH_2)(PNP)]$(BF_4)_2$ (**481**) reacted with water and methanol to give the alkyl complexes [Pt(CH_2CH_2OH)(PNP)]BF_4 (**735**) and [Pt(CH_2CH_2OMe)(PNP)]BF_4 (**736**), respectively, the mono-substituteted alkene complexes [Pt(CH_2=CHR)(PNP)]$(BF_4)_2$ (**737**, R = Ph; **738**, R = Me; **739**, R = Et; **740**, R = naphthyl) reacted regioselectively with MeOH to give the corresponding *β*-functionalized alkyl complexes [Pt($CH_2CHR(OMe)$(PNP)]$(BF_4)_2$ (**741**, R = Ph; **742**, R = Me; **743**, R = Et; **744**, R = naphthyl) (Scheme 130).[195,233] Similar results were obtained in the reactions of palladium complexes of the type [Pd(CH_2=CHR)(PNP)]$(BF_4)_2$ with water and methanol.[193]

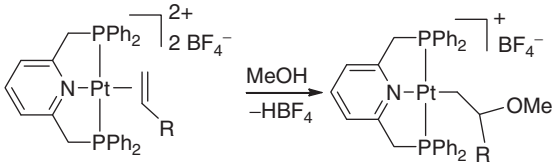
Nucleophilic attack of alcohols on the olefinic carbon also occurred in the reactions of the pivalamidate-bridged Pt(III) complex **166** with alkenes and alcohols. For example, the bimetallic complex **166** reacted with CH_2=$CH(CH_2)_3OH$ to give the alkyl complex **745**, and with cyclohexene in methanol to give the alkyl complex **747** (Scheme 131).[234,235]

Scheme 132 shows additional examples of nucleophilic addition of oxygen-based nucleophile to alkenes coordinated to platinum and palladium with other ligand environments. The cyclopentadienyl palladium complex [CpPd(CH_2CH_2OR)(PPh_3)]



481

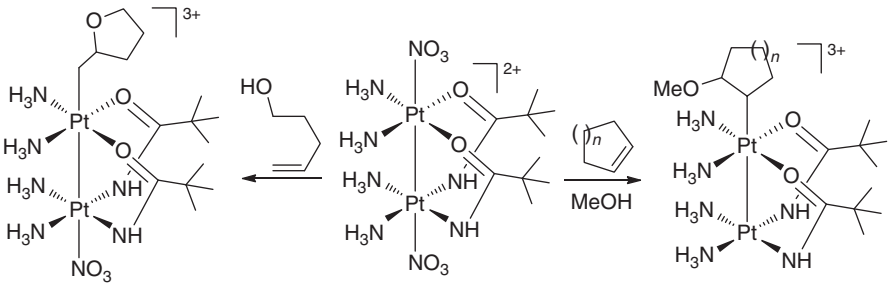
735, R = H (87%)
736, R = Me (82%)



737, R = Ph
738, R = Me
739, R = Et
740, R = Naphthyl

741, R = Ph (88%)
742, R = Me (85%)
743, R = Et (78%)
744, R = Naphthyl (87%)

Scheme 130

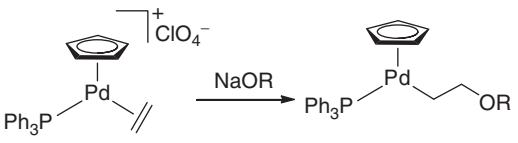


745 (63%)

166

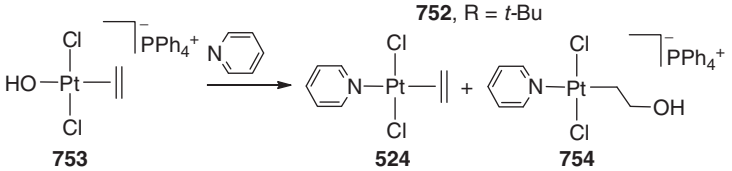
746, *n* = 1 (53%)
747, *n* = 2

Scheme 131



466

748, R = Me
749, R = Et
750, R = *n*Pr
751, R = *i*-Pr
752, R = *t*-Bu



753

524

754

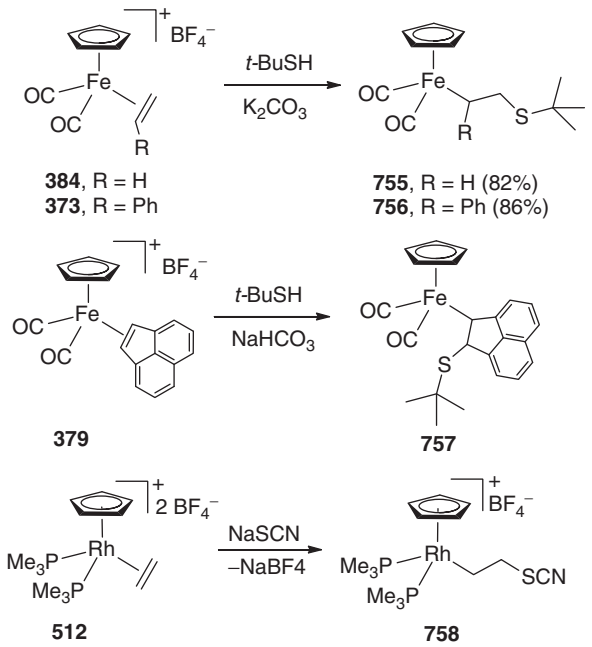
Scheme 132

ClO_4 (**466**) reacted with sodium alkoxides (NaOR) to give the alkyl complexes $CpPd(CH_2CH_2OR)(PPh_3)$ (e.g., **748–752**) (Scheme 132).[236] Reactions of the anionic complex $PPh_4[PtCl_2(OH)(CH_2{=}CH_2)]$ (**753**) with pyridine produced a mixture of the alkene complex $PtCl_2(CH_2{=}CH_2)$(pyridine) (**524**) and the alkyl complex $PPh_4[PtCl_2(OH)(CH_2CH_2OH)]$ (**754**). The alkyl complex **754** was thought to be formed by nucleophilic attack of OH^- on coordinated olefin ligand.[230]

4.10.3.4 Reactions with Sulfur-Based Nucleophiles

Only a few examples of nucleophilic addition of sulfur-based nucleophiles on coordinated alkenes have been documented.

The iron complexes $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ (**384**, R=H; **373**, R=Ph) reacted with *t*-butylsulfide in the presence of Na_2CO_3 to produce the alkyl complex $CpFe\{CH_2CHR(S\text{-}t\text{Bu})\}(CO)_2$ (**755**, R=H; **756**, R=Ph) (Scheme 133).[150] A similar reaction occurred between *t*-butylsulfide and the acenaphthylene complex **379** in the presence of $NaHCO_3$ to give the alkyl complex **757**. The rhodium ethylene complex $[(C_6H_6)Rh(PMe_3)_2(CH_2{=}CH_2)]PF_6$ (**512**) reacted with NaSCN to produce the alkyl complex **758**.[156]



Scheme 133

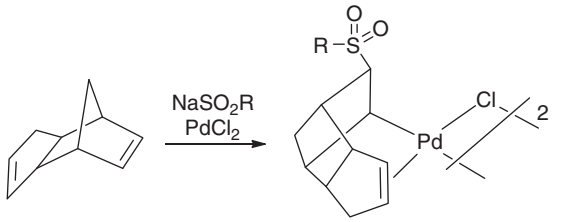
Alkylsulfinates can react as sulfur-nucleophiles with $PdCl_2$ and diolefins to give *trans*-sulfonyl-palladated complexes. For example, dicyclopentadiene reacted with $PdCl_2$ and $NaSO_2R$ (R=CMe_3, CH_2CPhMe) to give the enyl complexes **759** and **760**; 1,4-cyclooctadiene reacted with $PdCl_2$ and $NaSO_2R$ (R=CMe_3, CH_2CPhMe_2) to give the enyl complexes **761** and **762** (Scheme 134).[237]

4.10.3.5 Reactions of Phosphorus-Based Nucleophiles

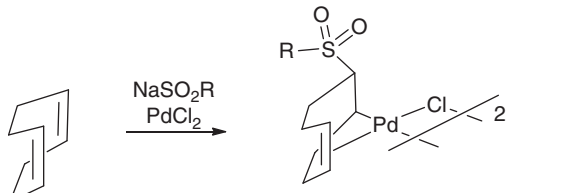
Nucleophilic addition of phosphines to coordinated alkene ligands have been reported for well-defined alkene complexes of group 6–10 metals.

Nucleophilic addition of phosphine to alkenes coordinated to group 6 metals was observed in the reactions of phosphines with the ethylene complexes $[CpM(CH_2{=}CH_2)(CO)_3]PF_6$ (M=Mo, W) and $[Cp_2WMe(CH_2{=}CH_2)]PF_6$. Treatment of the ethylene complexes $[CpM(CH_2{=}CH_2)(CO)_3]PF_6$ (**483**, M=Mo; **484**, M=W) with PPh_3 produced the alkyl complexes $[CpM(CH_2CH_2PPh_3)(CO)_3]PF_6$ (**763**, M=Mo; **764**, M=W) (Scheme 135).[148] The ethylene complex $[Cp_2WMe(CH_2{=}CH_2)]PF_6$ (**765**) reacted with PMe_2Ph to give the alkyl complex **766**.[238]

Several examples of addition of phosphines to alkene ligands coordinated to group 8 metals have appeared in the literature. Phosphorus addition reactions of $[CpFe(CH_2{=}CHR)(CO)_2]^+$ have been reported by Rosenblum et al. Treatment of the alkene complexes $[CpFe(CH_2{=}CHR)(CO)_2]BF_4$ (**384**, R=H; **372**, R=Me; **373**, R=Ph) with PPh_3 produced the alkyl complexes $[CpFe\{CH_2CHR(PPh_3)\}](CO)_2]BF_4$ (**767**, R=H; **768**, R=Me; **769**, R=Ph) (Scheme 136). The reaction of $[CpFe(CH_2{=}CH_2)(CO)_2]BF_4$ (**384**) with $Na[(MeO)_2PO]$ gave the alkyl complex **770**.[122]

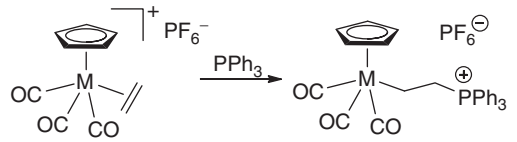


759, R = CMe_3 (82%)
760, R = CH_2CPhMe_2 (85%)



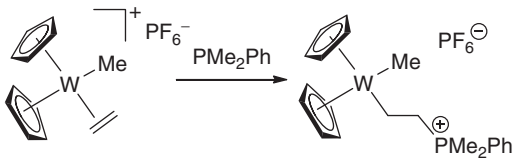
761, R = CMe_3 (87%)
762, R = CH_2CPhMe_2 (87%)

Scheme 134



483, M = Mo
484, M = W

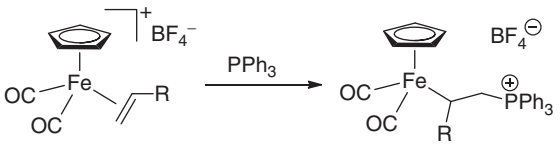
763, M = Mo (80%)
764, M = W (84%)



765

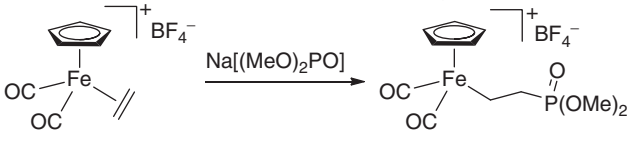
766 (70%)

Scheme 135



384, R = H
372, R = Me
373, R = Ph

767, R = H
768, R = Me
769, R = Ph

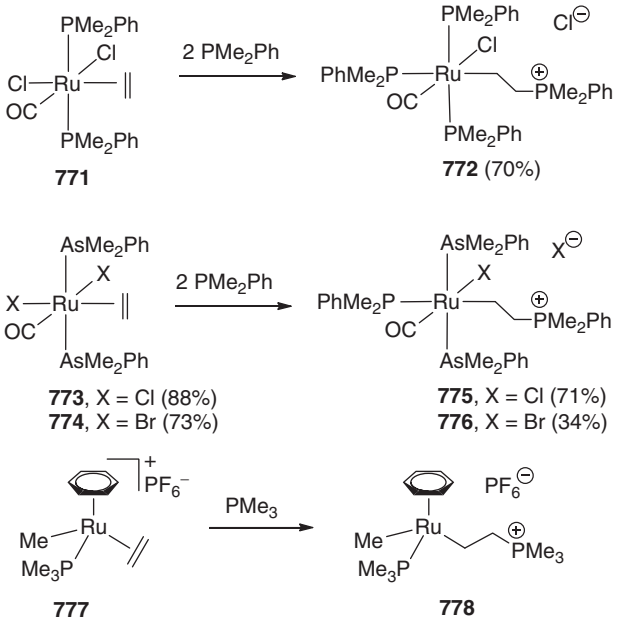


384

770 (41%)

Scheme 136

Attack of phosphines on alkene ligands coordinated to ruthenium has been described by Mawby and Werner. The ethylene complex $RuCl_2(CH_2{=}CH_2)(XMe_2Ph)_3$ (X=P, **771**; X=As, **773**) reacted with PMe_2Ph to give the alkyl complexes **772** and **775** (Scheme 137).[239] The ethylene complex $[(C_6H_6)RuMe(PMe_3)(CH_2{=}CH_2)]PF_6$ (**777**) reacted with PMe_3 to produce the alkyl complex **778**.[240]



771 **772** (70%)

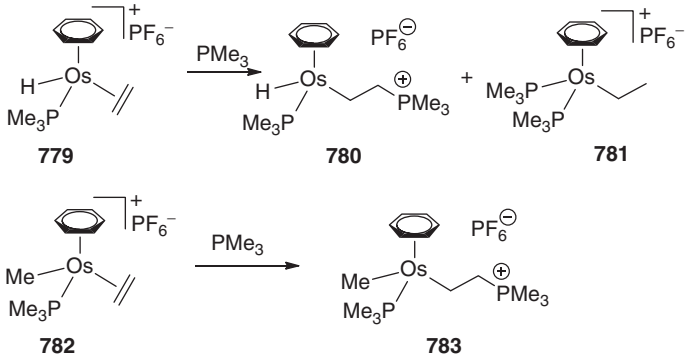
773, X = Cl (88%)
774, X = Br (73%)

775, X = Cl (71%)
776, X = Br (34%)

777 **778**

Scheme 137

The reactions of PMe_3 with the osmium complexes $[(C_6H_6)OsX(PMe_3)(CH_2{=}CH_2)]PF_6$ (**779**, X=H; **782**, X=Me) have been investigated by Werner and Werner. They have shown that the reaction of PMe_3 with $[(C_6H_6)OsH(PMe_3)(CH_2{=}CH_2)]PF_6$ (**779**) produced a mixture of the alkyl complexes **780** (from PMe_3 attack on $CH_2{=}CH_2$) and **781** (from a hydride insertion reaction) (Scheme 138). The reaction of PMe_3 with $[(C_6H_6)OsMe(PMe_3)(CH_2{=}CH_2)]PF_6$ (**782**) produced the alkyl complex **783** as a result of attack of PMe_3 on the $CH_2{=}CH_2$ ligand.[241]

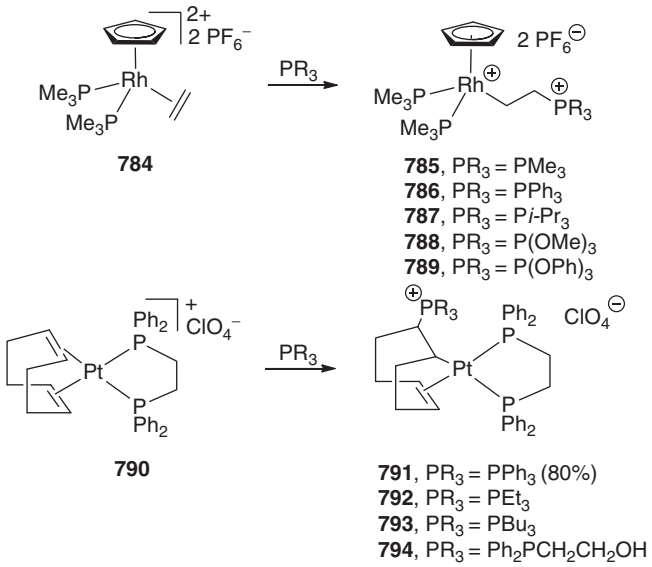


779 **780** **781**

782 **783**

Scheme 138

Scheme 139 shows examples of phosphine attack on alkenes coordinated to group 9 and 10 metals. Tertiary phosphines or phosphite attacked the $CH_2{=}CH_2$ ligand of $[(C_6H_6)Rh(PMe_3)_2(CH_2{=}CH_2)]PF_6$ (**784**) to produce the corresponding alkyl complexes (e.g., **785–789**) (Scheme 139).[156] Reactions of tertiary phosphines with $[Pt(COD)(dppe)]ClO_4$ (**790**) resulted in the formation of the enyl products **791–794** derived exclusively from attack of the phosphines on the coordinated dienes.[242]

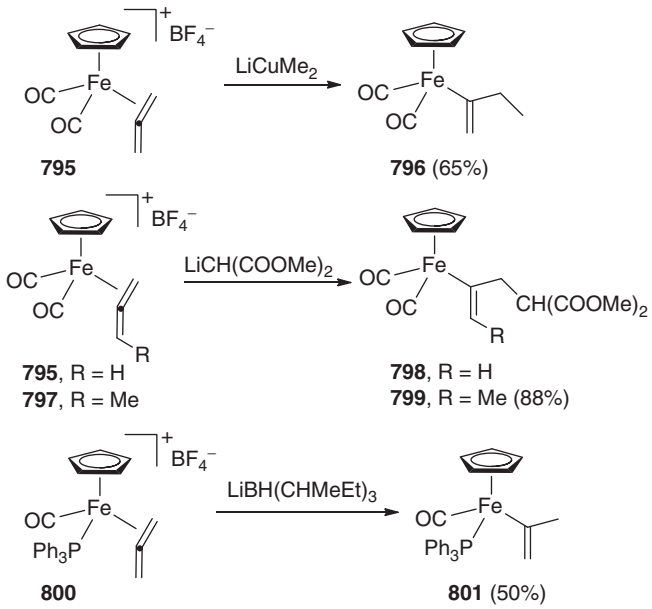


Scheme 139

4.10.4 Reactions of Allenes

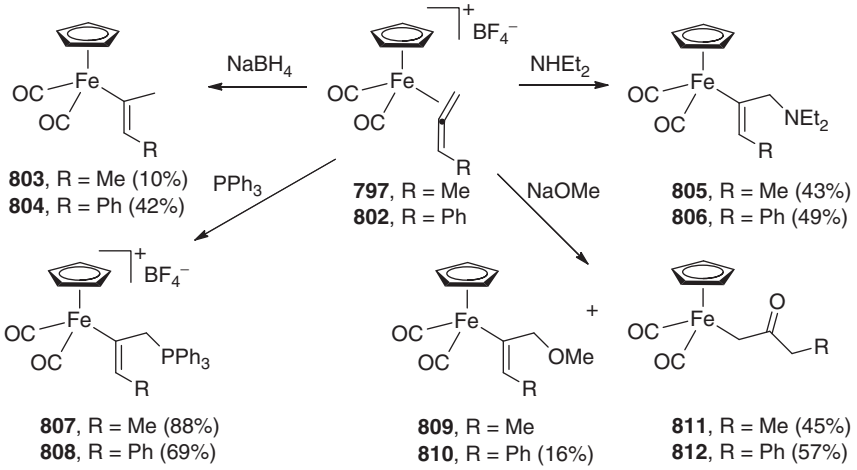
Nucleophilic addition reactions of coordinated allenes have been recognized as one of the key steps in catalytic addition reactions of allenes, for example, hydroamination[243] and hydroalkoxylation.[244] Stoichiometric nucleophilic addition to coordinated allene ligands has been reported for allene complexes of iron, palladium, platinum, and gold.

The allene ligands of $[CpFe(allene)(CO)(L)]^+$ can be attacked by a variety of nucleophiles to give vinyl complexes. For example, treatment of $[CpFe(CH_2{=}C{=}CH_2)(CO)_2]BF_4$ (**795**) with $LiCuMe_2$ produced the vinyl complex **796** (Scheme 140);[117] the reactions of $[CpFe(CH_2{=}C{=}CHR)(CO)_2]BF_4$ (**795**, R=H; **797**, R=Me) with $LiCH(COOMe)_2$ produced the vinyl complexes $CpFe\{(MeO_2C)_2CHCH_2C{=}CHR\}(CO)_2$ (**798**, R=H; **799**, R=Me);[117] the reaction of $[CpFe(CH_2{=}C{=}CH_2)(CO)(PPh_3)]BF_4$ (**800**) with L-Selectride gave the vinyl complex **801**.[26]



Scheme 140

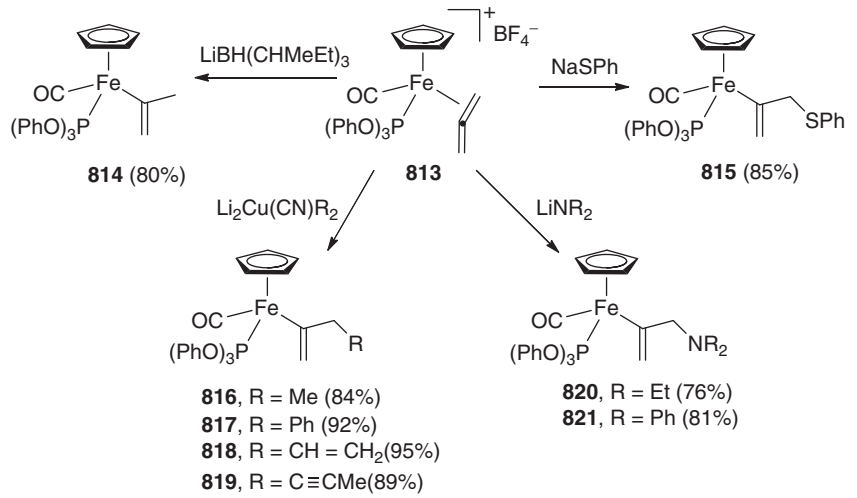
Reactions of the allene complexes $[CpFe(CH_2{=}C{=}CHR)(CO)_2]BF_4$ (**797**, R=Me; **802**, R=Ph) with nucleophiles have been studied by Wojcicki and coworkers.[245] They found that these complexes reacted with $NaBH_4$, $NHEt_2$, and PPh_3 at the terminal CH_2 carbon to give the corresponding vinyl complexes **803–808** (Scheme 141). When NaOMe was used, the reactions produced the



Scheme 141

vinyl complexes $CpFe(MeOCH_2C{=}CHR)(CO)_2$ (**809**, R=Me; **810**, R=Ph) and the *β*-ketonyl complexes $CpFe(CH_2C(O)CH_2R)(CO)_2$ (**811**, R=Me; **812**, R=Ph).

The reactions of the allene complex $[CpFe(CH_2{=}C{=}CH_2)(CO)(P(OPh)_3)]BF_4$ (**813**) with anionic nucleophiles have been studied by Reger et al.[29,33] They found that the allene complex **813** reacted with L-Selectride and NaSPh to give the vinyl complexes $CpFe(CH_3C{=}CH_2)(CO)_2$ (**814**) and $CpFe(PhSCH_3C{=}CH_2)(CO)_2$ (**815**), respectively. The complex also reacted with cuprates Li_2CuR and amides $LiNR_2$ to give the vinyl complexes $CpFe(RCH_2C{=}CH_2)(CO)_2$ (e.g., **816–819**) and $CpFe(R_2NCH_2C{=}CH_2)(CO)_2$ (**820–821**), respectively (Scheme 142).

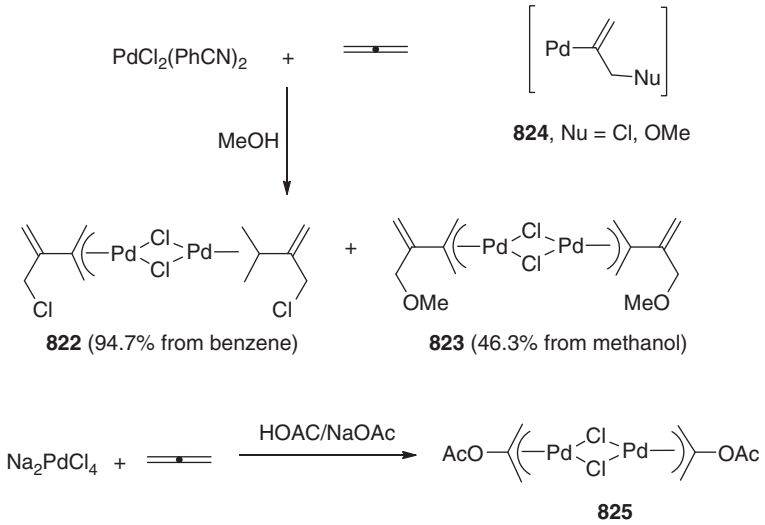


Scheme 142

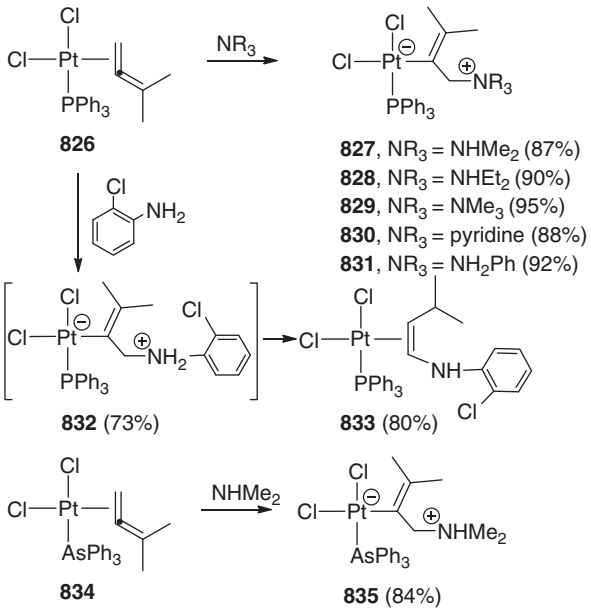
Nucleophilic attack of coordinated allenes coordinated to palladium probably occurred in the reaction of $PdCl_2(PhCN)_2$ with 1,2-propadiene in methanol. The reaction produced the two bimetallic allyl complexes **822** and **823** (Scheme 143).[246] In these reactions, the **822** and **823** can be thought as being formed by insertion of 1,2-propadiene into the Pd–C bonds of the vinyl palladium intermediates **824** formed by external attack of coordinated 1,2-propadiene by Cl^- or methanol. It has also been reported that the reaction of 1,2-propadiene with Na_2PdCl_4 in acetic acid in the presence of NaOAc produced the 2-acetoxy allyl complex **825**, because of nucleophilic attack of OAc^- on the central carbon of allene.[247]

Several stoichiometric nucleophilic addition reactions of amines have been demonstrated with platinum allene complexes. The platinum complex $PtCl_2(CH_2{=}C{=}CMe_2)(PPh_3)$ (**826**) reacted with aliphatic and aromatic amines to give zwitterionic alkenyl complexes (e.g., **827–831**) (Scheme 144).[248] Interestingly, addition of 2-chloroaniline to the allene complex **826** produced the enamine complex **833**, presumably through isomerization of the zwitterionic alkenyl intermediate **832**.[249] The analogous complex $PtCl_2(CH_2{=}C{=}CMe_2)(AsPh_3)$ (**834**) reacted similarly with $NHMe_2$ to give complex **835**.

Reactions of amines with the allene complex $PtCl_2(CH_2{=}C{=}CH_2)(PPr_3)$ (**836**) have also been described. The complex **836** reacted with NR_3 (R=Me, Et) to produce the zwitterionic alkenyl complexes **837–838** (Scheme 145). The reaction of **836** with a



Scheme 143

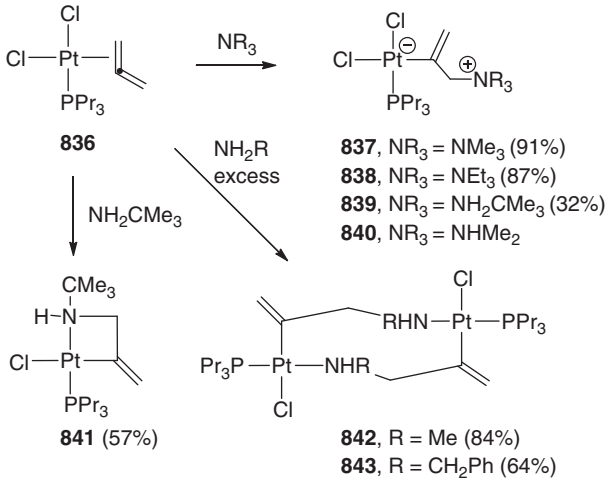


Scheme 144

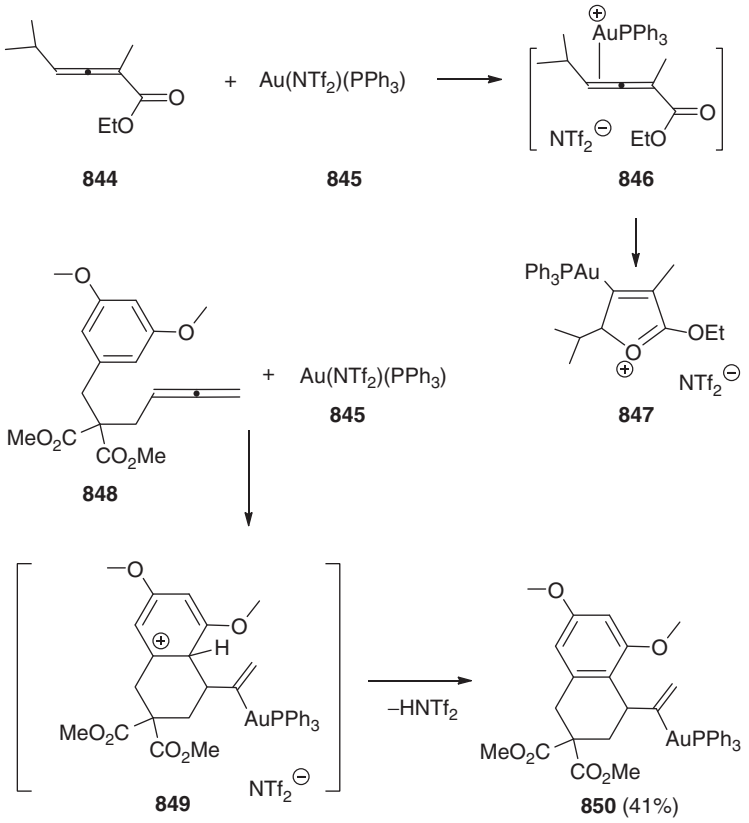
limiting amount of NH_2CMe_3 also produced the analogous zwitterionic alkenyl complex **839**. When excess NH_2CMe_3 was used, the reaction produced the four-membered metallacyclic complex **841**. Reactions of **836** with excess of other primary amines RNH_2 (e.g., R=Me, $PhCH_2$) produced eight-membered bimetallic complexes (e.g., **842–843**).[250]

Vinylgold compounds have been proposed as reactive intermediates in gold-catalyzed nucleophilic addition reactions of allenes. A few of such species have been isolated experimentally.[251] The gold(I) complex $Au(NTf_2)(PPh_3)$ (**845**) reacted with ethyl 2,5-dimethylhexa-2,3-dienoate (**844**) to give the di(alkoxy)carbenium ion **847** as a result of intramolecular nucleophilic O-attack on coordinated allene of the intermediate **846**.[252] In a related study, the vinylgold complex **850** was isolated from the reaction of the allene **848** with $Au(NTf_2)(PPh_3)$, which is presumably formed via the intermediate **849** formed by an intramolecular nucleophilic addition reaction (**Scheme 146**).[253]

$AuCl(PPh_3)$ reacted with ethyl α-methyl-γ-(n-hexyl)-allenoate (**851**) in dichloromethane in the presence of AgOTf at room temperature to give the vinylgold complex **854** (**Scheme 147**).[254] The vinyl complex **854** is likely formed by intramolecular nucleophilic attack of carbonyl on coordinated allene of the intermediate **852** to give the ionic species **853**, followed by hydrolysis.



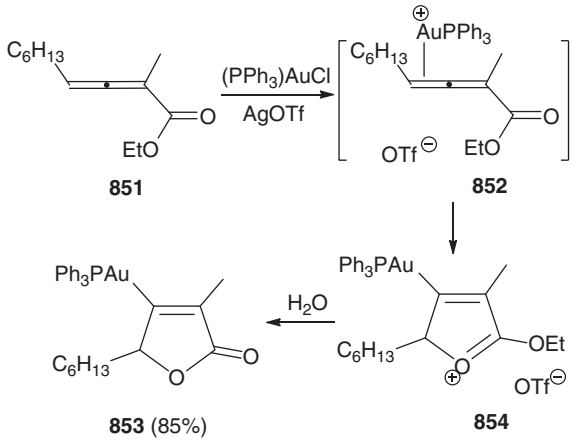
Scheme 145



Scheme 146

4.10.5 Summary

Nucleophilic addition reactions of coordinated alkynes, alkenes, and allenes have been intensively studied because of their importance for the transformation or functionalization of these unsaturated hydrocarbons. Numerous examples of stioichiometric nucleophilic addition reactions of coordinated alkynes, alkenes, and allenes have been documented especially for reactions involving middle/late transition metals and carbon-, nitrogen-, oxygen-, sulfur-, halogen-, and phosphorus-based nucleophiles. Nucleophilic addition to two-electron-donor alkyne ligands usually produces *trans*-η^1-vinyl complexes, and reactions involving



Scheme 147

four-electron-donor alkyne ligands yield η^2-vinyl (or metallacyclopropene) complexes. Nucleophilic addition to η^2-alkene ligands usually produce alkyl complexes. Reactions of η^2-allene ligands can produce either vinyl or allyl complexes. These reactions can play a very important role in catalytic reactions mediated by transition metal complexes. They can also be used for organic synthesis involving stioichiometric amount of reagents. Further development in the applications of the chemistry in organic synthesis is expected.

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4.11 Nucleophiles with Allyl Metal Complexes

C-H Ding and X-L Hou, Chinese Academy of Sciences, Shanghai, China

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Glossary

Allyl metal complex The metal complex has an allyl ligand. Allyl ligand binds to metal either via all three carbon centers, the so-called η^3-binding mode, or via only the methylene group, the so-called η^1-binding mode.

Enantiomeric excess (*ee*) The excess of one enantiomer over the other in a mixture of the two.

Leaving group The atom or group of atoms that departs during a substitution or elimination reaction.

Ligand The various ions, atoms, or neutral molecules that surround and are directly bonded to a central atom, usually a metal atom.

Nucleophile An electron pair donor. Molecules or ions with an unshared pair of electrons or a π bond can act as nucleophiles.

Substitution A reaction in which an attacking species of one type (nucleophile, electrophile, or free radical) replaces another group of the same type.

4.11.1 Introduction

Allyl metal complexes are one of the most common classes of organometallic compounds. Various metals, such as Pd, Ir, Ni, Cu, Fe, Ru, Rh, Mo, W, Pt, etc., can form π-allyl metal complex, which may react with a variety of nucleophiles and have received continuing attention of the synthetic chemistry community in the past half century.[1] Usually, the allyl metal complexes can be formed *in situ* and the metal catalyst can be regenerated. These features enable the reaction to require only catalytic amounts of metal catalyst. The focus has shifted to metal-catalyzed enantioselective allylic substitution with nucleophiles since 1990s. These reactions proceed under mild reaction conditions, and good chemo-, regio-, and enantioselectivities. These unique advantages

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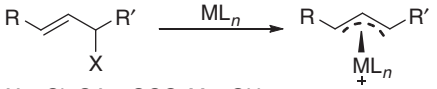
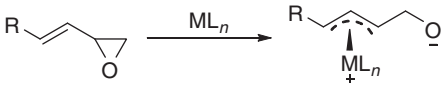
make the reaction become one of the most useful reactions to fabricate C–C and C–X bond and find wide applications in the total synthesis of natural products, pharmaceuticals, fine chemicals, and complex molecules.[2] In this review, such advances since 1990 will be summarized. Some earlier works will be mentioned if necessary. The applications of the reaction in the synthesis of natural products will also be included.

4.11.1.1 Methods for Generating Allyl Metal Complexes

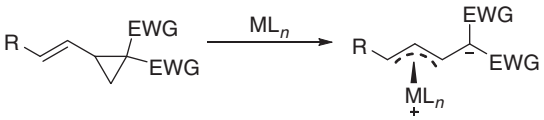
The most common way to generate an allyl metal complex is by oxidative addition of metal to allyllic compound bearing a leaving group. The leaving group could be an acetate, carbonate, phenol, tertiary amine, nitro, halide, sulfonyl, etc. (equations 1–3).[3] The process involves the initial coordination of the metal to the olefin moiety of the allyl compound, followed by ionization of the allylic leaving group to form a new π-allyl metal complex.



X = Cl, OAc, OCO_2Me, OH, OCONHMe, $OP(O)(OMe)_2$, NO_2, SO_2Ph or NR_3Cl. (1)

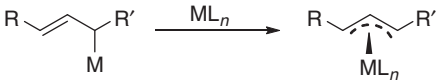


(2)



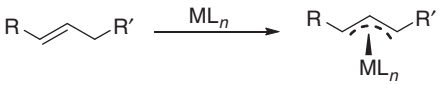
(3)

The transmetallation of an allyl metal compound by another metal complex is also an efficient access to furnish a π-allyl metal complex (equation 4).



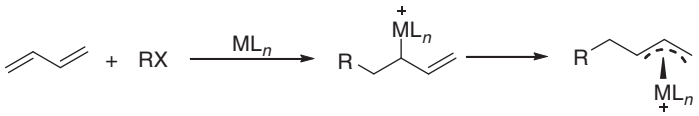
M = B or Sn (4)

The removal of an allylic hydrogen from olefin by a metal salt is the most direct route to a π-allyl metal complex (equation 5). For these transformations, the palladium salts are the most efficient catalyst.[4] Allylic C–H functionalization using Pd catalyst has become one of the research hotspots recently.

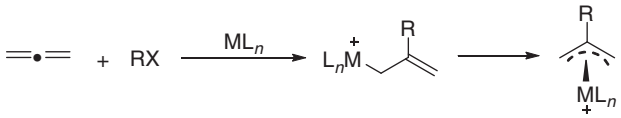


(5)

The reaction of organic halides with 1,3-dienes or allenes in the presence of a metal catalyst can also form the π-allyl metal complex (equations 6 and 7).[5]



(6)

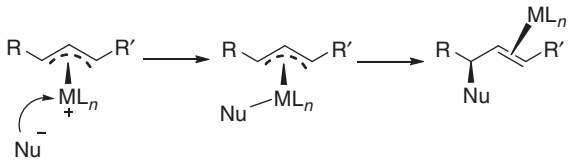


(7)

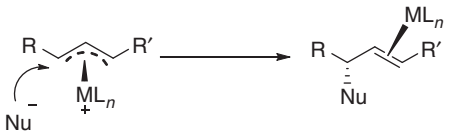
4.11.1.2 General Reaction Mode of Allyl Metal Complexes with Nucleophiles

The reaction of allyl metal complexes with nucleophiles can proceed through several distinct pathways.[6] The nucleophile may first attack the metal center followed by subsequent reductive elimination to form the new bond (equation 8). This type of process

results in the retention of stereochemistry of the allyl metal complex. Usually, 'hard' nucleophiles typically react through this way. Alternatively, the nucleophile can attack the terminal allylic carbon directly, opposite from the face where the metal resides, which results in the inversion of stereochemistry from the metal allyl complex (equation 9). The 'soft' nucleophiles prefer this type of attack.

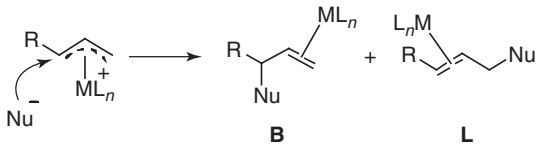


(8)

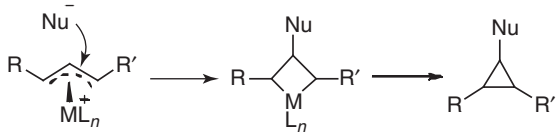


(9)

In the case of monosubstituted π-allyl metal complex, the nucleophile may attack the C-3 with substituent to furnish the branched product (**B**), or it attacks the unsubstituted terminus C-1 to give the linear product (**L**) (equation 10). This regioselectivity is usually controlled by the transition metal. In general, the π-allyl metal complexes derived from Pd,[3] Fe,[7a] Ni[7b,c] give the linear products, whereas those derived from Ir,[8] Rh,[9] W,[10] or Mo,[11] Ru,[12] Pt[13] give the branched products. However, regioselectivity can also be controlled in Pd-catalyzed reactions using specially designed ligands or in the reactions using *N*-nucleophiles, including an unprotected aziridine,[14] hydrazine, and hydroxylamine.[15] Nucleophiles may also attack the central carbon of π-allyl to afford a palladacyclobutane in some cases, which is converted into the cyclopropane by reductive elimination (equation 11).[16]



(10)



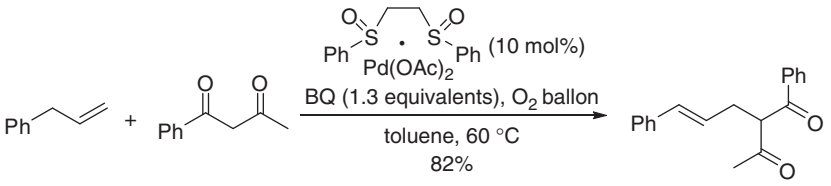
(11)

4.11.2 Carbon Nucleophiles

The carbon nucleophiles have been extensively used in the reaction with allyl metal complexes. The reaction is applicable to a variety of carbon nucleophiles such as enolates derived from ketones, carboxylic acid derivatives, malonates, and organometallic reagents. Chemoselectivity as well as regio- and enantioselectivities can be controlled in many cases.

4.11.2.1 Stablized Carbon Nucleophiles

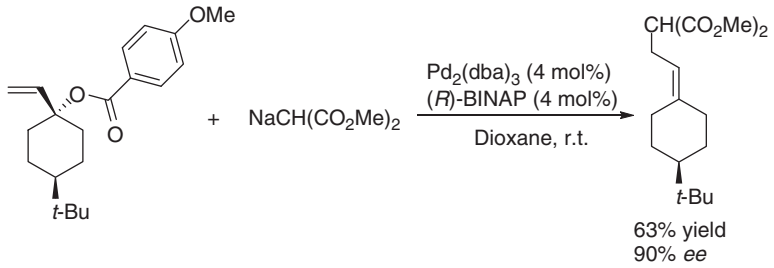
Malonate and acetoacetate were the first kinds of stablized carbon nucleophile used in the reaction with π-allylpalladium chloride reported by Tsuji and coworkers in 1965.[17] This pioneering work, nowadays named as Tsuji–Trost reaction, clearly shows the electrophilicity of the π-allylpalladium complexe and opens the way for the study of nucleophilic reaction with allyl metal complexes as well as their applications in organic synthesis. Usually, a functional group at the allylic position is required to serve as a reacting and leaving group. In 1973, Trost and coworkers observed that π-allylpalladiumcomplex might be formed directly from olefin, which smoothly underwent the alkylation reaction with malonate anion.[4] However, a catalytic version of such directed formation of π-allylpalladium complex via allylic C–H activation had not been realized for more than 30 years. It may be attributed to the difficulty of *in-situ* reoxidation of Pd(0) into Pd(II). In 2008, two groups independently addressed the challenges using sulfoxide and Pd(II) as catalyst and benzoquinone (BQ) as oxidant. Shi and coworkers achieved the direct coupling of a 1,3-dicarbonyl compounds with a terminal olefin via allylic C–H activation using $Pd(OAc)_2$/bis-sulfoxide catalyst, which was developed by White's group (equation 12).[18] Simultaneously, with very similar reaction conditions, White and coworkers realized intermolecular allylic alkylation of allylarenes with nitroacetate.[19] In White's case, the addition of dimethylsulfoxide (DMSO) and AcOH is crucial for the reaction. DMSO was ever reported to activate π-allyl-Pd complexes toward alkylation with malonates.[20]



(12)

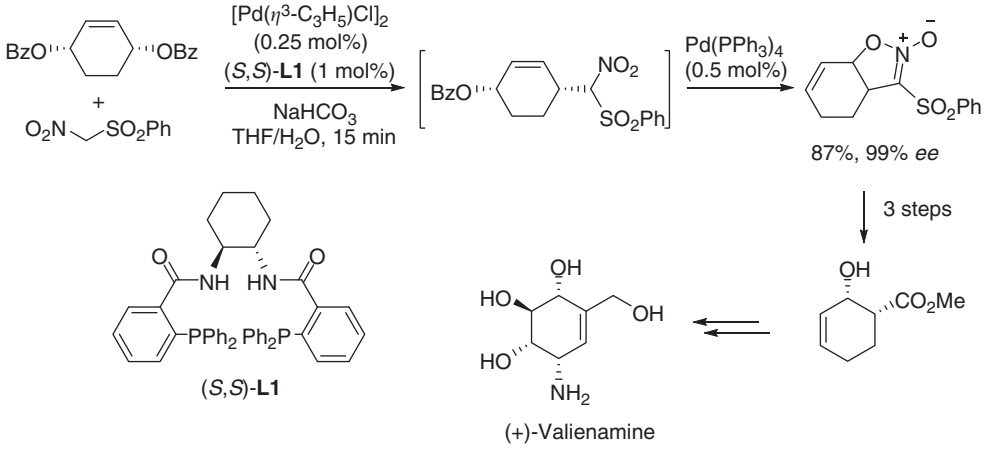
A catalytic asymmetric reaction of malonate nucleophile with allylic compounds through π-allyl-Pd intermediates was firstly reported by Trost group in 1977.[21] Since then, the reaction of nucleophile with allyl metal complex in the catalytic asymmetric manner has become a very active research area. Before 1990, the enantioselectivity of such reaction was usually not high.[22] Tremendous progress had been accomplished with a lot of newly developed chiral ligands in 1990s.

Sodium dimethyl malonate was reported to react with vinylcyclohexyl 4-methoxybenzoate using palladium/(*R*)-2,2′-bis (diphenylphosphino)-1,1′-binaphthalene (BINAP) catalyst to give the product with 90% *ee* (equation 13).[23] The stereochemical results of the reaction indicated that the step determining the enantioselectivity of the reaction was the oxidative addition of the allylic substrate onto the chiral Pd complex, which was strongly influenced by the nature of the leaving group in allylic derivatives. The solvent also had a substantial effect on the selectivity of the reaction. The use of toluene as a solvent or the addition of crown ethers resulted in the drop of product enantioselectivity.



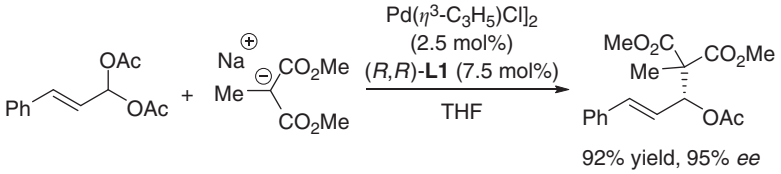
(13)

Trost reported the Pd-catalyzed reaction of (phenylsulfonyl)nitromethane and dibenzoate with chiral 2-(diphenylphosphino) aniline chiral ligand (Trost's Ligand **L1**). The product of double alkylation, the isoxazoline *N*-oxides, was afforded in 98% *ee*.[24] Several years later, the reaction on a larger scale was realized by performing the reaction in 3:1 tetrahydrofuran (THF)-water rather than in pure THF (**Scheme 1**).[25] The first alkylation completes within 15 min with 0.25 mol% of the palladium catalyst. The second stage of the *O*-alkylation leading the isoxazoline *N*-oxide is much slower due to the requirement of a 'mismatched' ionization. The addition of tetrakis(triphenylphosphine)palladium is proved to be effective to accelerate cyclization. The resultant isoxazoline *N*-oxide was obtained in 87% yield with >99% *ee*, which is a useful intermediate in the enantioselective synthesis of (+)-valienamine via the chiral *cis*-β-hydroxyester.



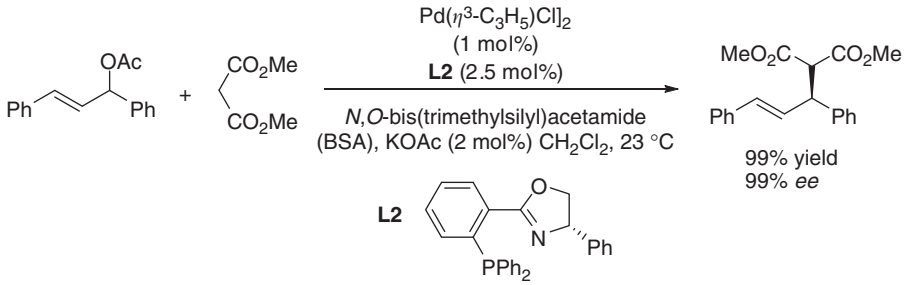
Scheme 1

Compared with the extensively studied reaction of malonate with allylic acetates catalyzed by Pd catalysis, the reaction with allyl substrates having two leaving groups on the same carbon atom at the allylic position is much less explored. Lu and Huang firstly disclosed such reaction under the catalysis of $Pd(PPh_3)_4$.[26] Ten years later, an asymmetric version was reported by Trost's group using the Pd/**L1** catalyst, which could effectively differentiate two enantiotopic leaving groups (equation 14).[27] The reaction is an alternative for asymmetric additions of stabilized nucleophile to carbonyl compounds.



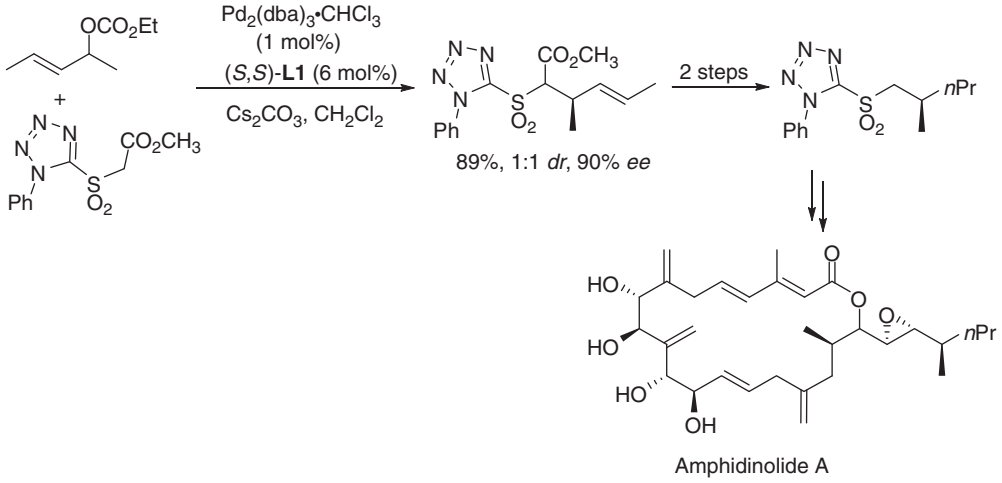
(14)

The alkylation reaction of 1,3-diphenylallyl acetate with malonate is a benchmark reaction to test the asymmetric induction of chiral ligand with Pd catalyst. Early results were reported by Trost employing (*R*)-BINAP as the ligand.[28] Since then, a variety of chiral ligands with different coordinated atoms based on various frameworks were created and applied in the reaction; many excellent results have been provided.[1] (Phosphinoaryl)oxazolin ligand (**L2**) is the earliest example giving diarylallyl adducts with excellent enantioselectivity (equation 15).[29]



(15)

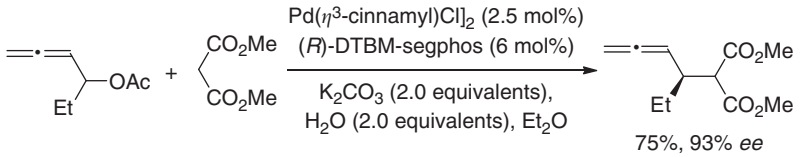
Malonate anion also participates in an alkylation reaction with 1,3-dialkyl allyl substrates using Pd catalysts. Asymmetric induction was realized in the presence of chiral ligands.[29a,30] Compared with 1,3-diaryl allyl substrates, the enantioselectivity was usually lower. The issue was addressed by the Trost group using chiral pocket ligand (**L1**).[31a] The choice of both the solvent and the alkali metal base is important. The use of THF as the solvent or NaH as the base dramatically decreased the *ee* value. The nucleophile was extended to a sulfone ester containing a tetrazole group.[31b] The alkylation product was provided as a 1:1 mixture of diastereomers in 89% yield and 90% *ee* (**Scheme 2**), which was elaborated further via decarboxylation and hydrogenation to construct the side chain of amphidimolide A.



Scheme 2

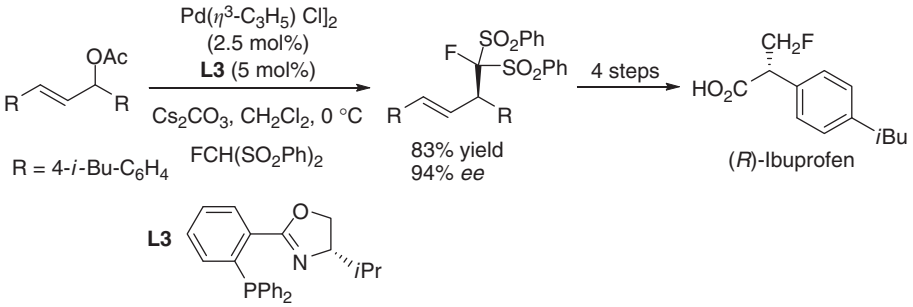
Malonate is able to react with (methylene-π-allyl)palladium species. Goré and coworkers reported the first example of a palladium-catalyzed reaction of sodium ethylmalonate with α-allenic acetates and α-allenic phosphates, leading exclusively to β-allenic malonates in 1984. The researcher proposed (methylene-π-allyl)palladium as the reaction intermediate.[32a,b] Later, Hayashi et al. disclosed a Pd-catalzyed synthesis of functionalized allenes from readily available 2-bromo-1,3-butadienes. The catalytic cycle of the allene formation reaction was established and the (methylene-π-allyl)palladium key intermediate was isolated and characterized.[32c] On the basis of these pioneering works, Pd-catalyzed asymmetric allylic alkylation (AAA) of 2,3-allenyl derivatives with malonate nucleophiles was realized, many of which afforded axially chiral allenes in excellent enantioselectivity.[32d–i] Ma and coworkers reported on a Pd-catalyzed asymmetric synthesis of optically active 2-(2,3-alkadienyl)malonates with central chirality in the allene chain by reaction of racemic 2,3-allenyl acetates with diethyl malonate (equation 16). The challenge arises from

differentiation of the relatively similar propadienyl and R groups. The use of a commercially available ligand (*R*)-di(3,5-di-*t*-butyl-4-methoxyphenyl) (DTBM)-segphos addressed this issue. The investigation into the factors dictating the enantioselectivity indicates that high enantioselectivity is mainly influenced by 4,4′-bibenzo[d][1,3]dioxole unit together with the bulky $C_6H_2(m\text{-}t\text{Bu})_2(p\text{-OMe})$ group, and the electron-rich nature of the phosphorus atoms results in the high catalytic activity.[32j]



(16)

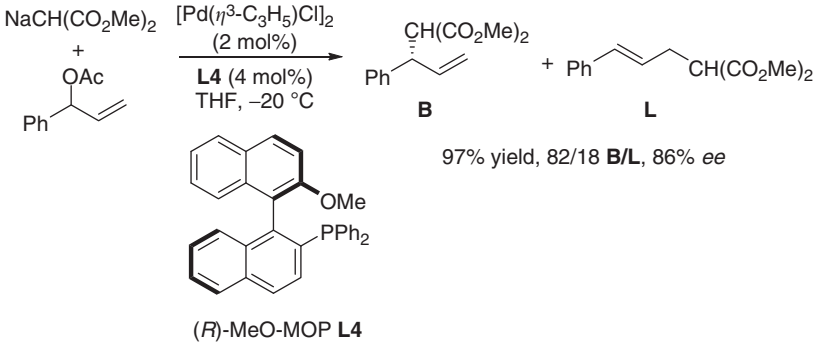
Fluorobis(phenylsulfonyl)methane (FBSM), a fluoromethide equivalent, is a suitable nucleophile for the alkylation reaction with allyl acetates using Pd catalyst (Scheme 3).[33] The product with high enantioselectivity was obtained in the presence of chiral ligand **L3**, which was converted into enantiopure monofluorinated ibuprofen in a highly efficient manner. An iridium catalyst could catalyze the regioselective alkylation reaction of FBSM with 1,3-unsymmetrical allylic substrates, affording the enantiopure fluorobis(phenylsulfonyl)methylated compounds.[34]



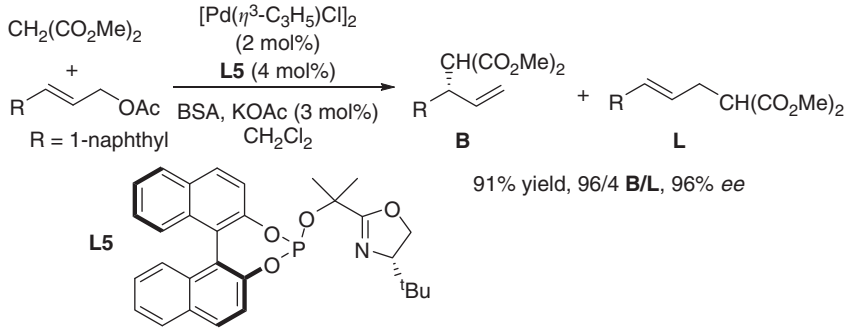
Scheme 3

The reaction of stabilized nucleophiles with monosubstituted allyl compounds catalyzed by a transition metal catalyst is much different from that with 1,3-disubstituted, simple allyl, and cyclic allyl substrates. The reaction may give linear or branched allylation products by the attack of nucleophile to different terminal carbon of the targeted η^3-ally-metal complex. Usually, linear and nonoptically active regioisomer is the major product due to the steric hinderance of allylic electrophile when Pd-complexes are the catalyst. Many other metal complexes, such as Ir, Rh,W, or Mo, prefer to give branched isomers via attacking the more hindered terminus.[8–11]

However, the reaction of malonate with some monosubstituted allyl substrates in the presence of Pd catalyst was able to afford branched isomers in high enantioselectivities using specially designed ligands. Hayashi found that 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ligand (MeO-MOP) **L4** gave good regio- and enantioselectivity in palladium-catalyzed alkylation, but with narrow substrate scope (equation 17).[35] Pfaltz developed phosphite oxazoline ligand **L5** and used them to control the regio- and enantioselectivity in the palladium-catalyzed allylic alkylation.[36] High regio- and enantioselectivity were achieved for 3-(1-naphthyl)-3-allylic acetate (equation 18). However, only moderate to low regioselectivity was obtained for other aryl- and alkyl-substituted substrates.

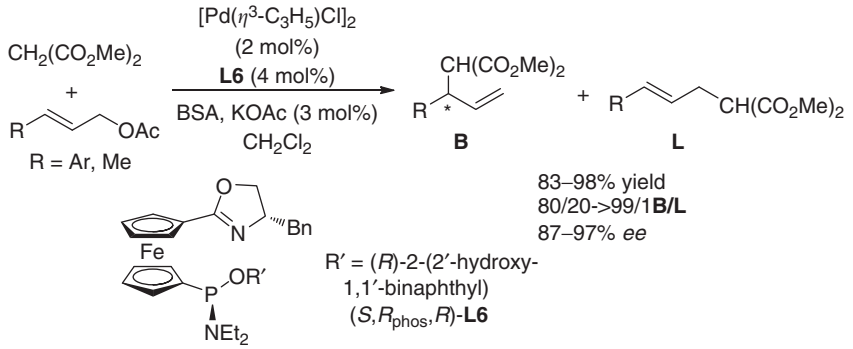


(17)



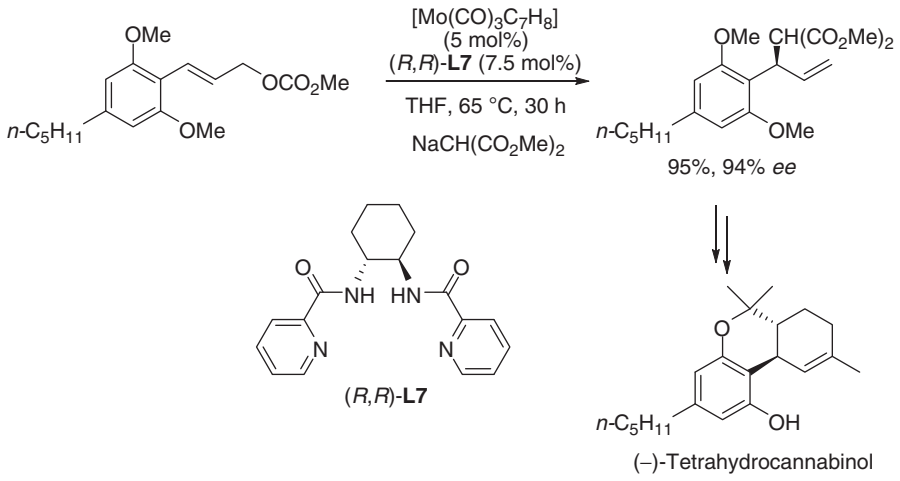
(18)

In 2001, Dai and Hou developed a chiral ferrocene-based ligand, SiocPhox **L6**, which afforded optically active branched products for a wide range of allyl substrates in up to 99/1 of B/L ratio with 87–97% *ee* (equation 19).[37] Chiral iridium complexes was able to catalyze the allylic alkylation of linear allylic carbonates with malonate to generate branched substitution products.[8] The malonate underwent nucleophilic substitution of optically enriched, branched allylic carbonates with retention of configuration under the effect of rhodium catalysts.[9]



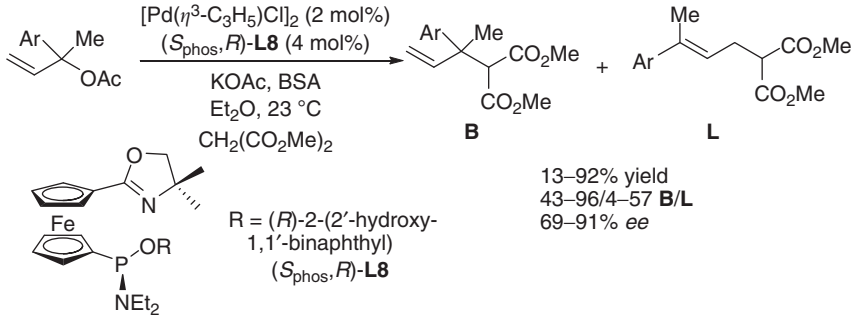
(19)

The reaction of sodium dimethyl malonate with a particularly sterically hindered allyl carbonate bearing a 2,4,6-trisubstituted aryl ring proceeded readily in the presence of $[Mo(CO)_3C_7H_8]$ and chiral ligand (*R,R*)-**L7** (Scheme 4).[38] Only the branched product was obtained in 95% yield and 95% enantiomeric excess, which was applied to the synthesis of (−)-tetrahydrocannabinol.



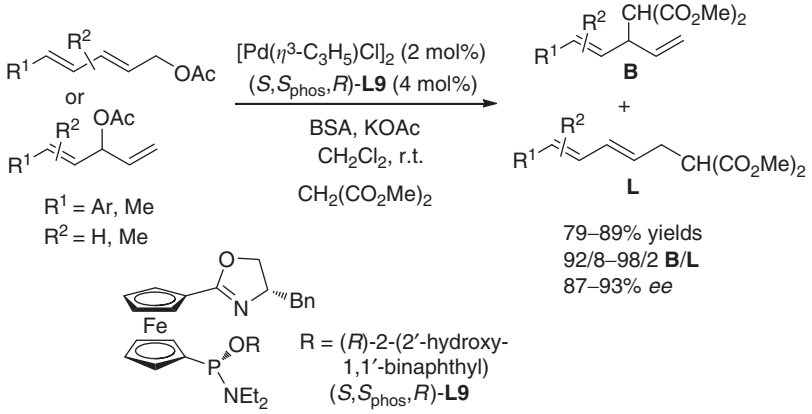
Scheme 4

Quaternary carbon center can be formed in the reaction of stabilized nucleophiles and 1,1-disubstituted allyl substrates with Pd catalysis. A major challenge of the reaction is controlling the attack at a sterically hindered position of allyl substrate. Using a modified SiocPhox ligand **L8**, Hou et al. succeeded in the reaction of substituted allyl acetates with malonate ester to install all carbon chiral quaternary carbon center with high regio- and enantioselectivities, B/L ratio being 43–96/4–57, and enantioselectivity being 69–91 for a wide range of allyl substrates (equation 20).[39]



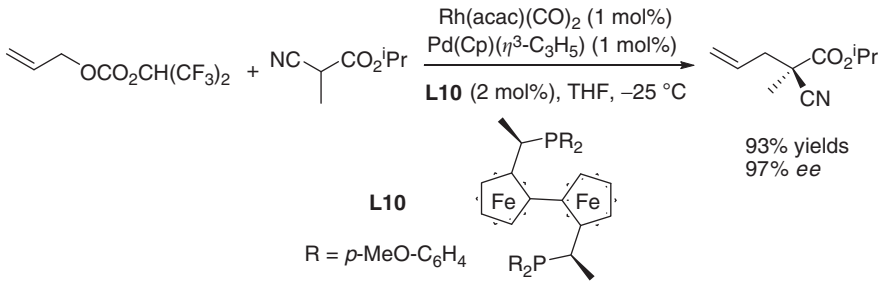
(20)

The polyenyl esters are special variant of monosubstituted allylic esters, whose reaction with malonate usually provided linear products under the effect of Pd catalysis. Hou group realized high regio- and enantioselective allylic alkylation reactions of polyenyl esters using their ferrocene-based chiral ligand **L9**, with B/L ratio ranging from 92/8 to 98/2 and enantioselctivity being 87–93% (equation 21).[40] Some metal complexes, such as Mo[11] and Ir,[41] are also efficient catalysts to realize regio- as well as enantioselectivities of allylic substitution reactions of polyenyl esters.



(21)

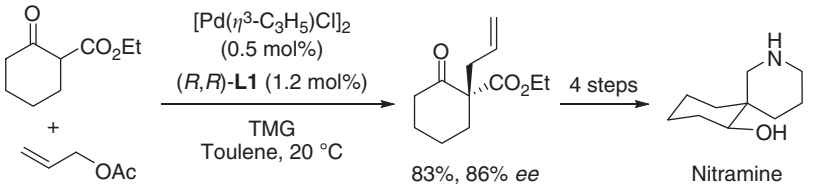
As nucleophile resides very distant to the chiral ligands in the transition state, control of the stereochemistry at nucleophile is much difficult in the reaction of allyl compound catalyzed by chiral transition metal complexes. Kagan and coworkers reported the first example of allylation reaction installing a chiral center at the nucleophile in 1978, but enantioselectivity of the allylated products was less than 10% *ee*.[42] The breakthrough came 10 years later with 1,3-diketone as substrate using chiral palladium complexes bearing ferrocenyl phosphine ligands as catalysts.[43] Sawamura and Ito offered an alternative solution to address the problem, which relied on the combination of two different transition metal complexes. One of the catalysts, a chiral rhodium complex, activated pronucleophiles, *α*-cyanoesters, thereby bringing the chiral ligands more proximal to the nucleophilic center and making the reaction occurring in an enantioselective manner (equation 22).[44]



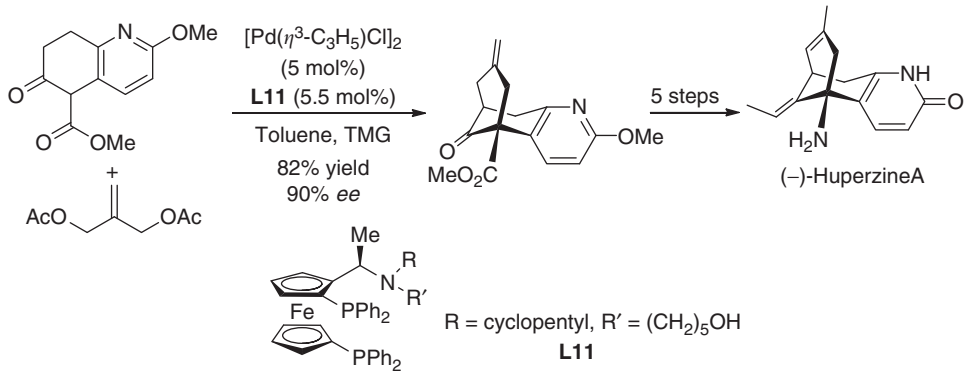
(22)

Trost et al. employed cyclic *β*-ketoesters as nucleophiles for the Pd-catalyzed allylic alkylation in the presence of the chiral pocket ligand **L1**, which permitted its chirality to be transmitted to the nucleophile efficiently (Scheme 5).[45] The reaction led to an asymmetric synthesis of spiro-alkaloid nitramine.

Reaction of *β*-ketoester with bifunctional allylic agent provided tricyclic intermediate in 90% *ee* through a bicyclic annulation manner using a chiral ferrocenyl phosphine ligand **L11** (Scheme 6).[46] This allylation product was elaborated further to enantiopure (−)-huperzine A, a Lycopodium alkaloid isolated from the Chinese herb *Huperzia serrata*, which was approved in China as a new drug for the treatment of Alzheimer's disease.

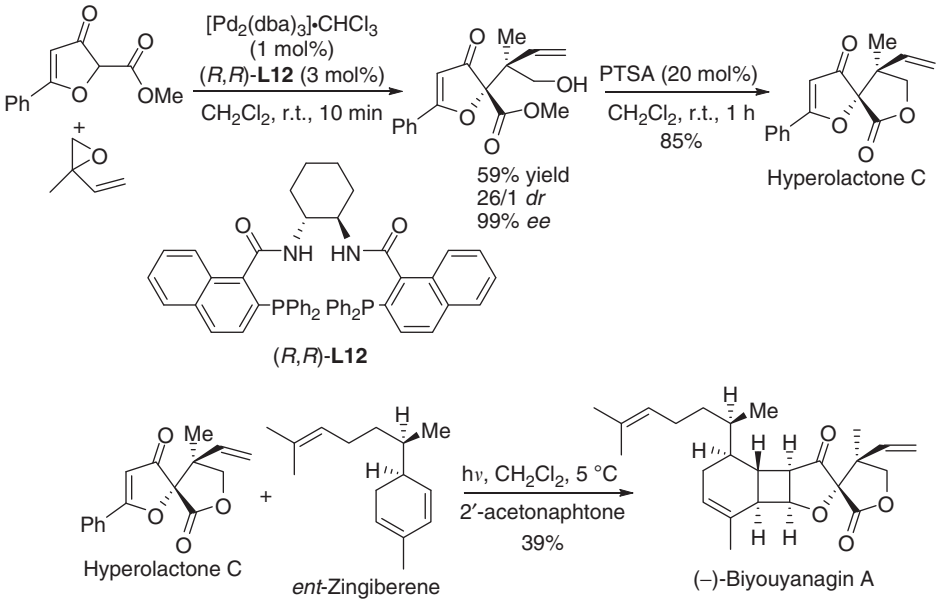


Scheme 5



Scheme 6

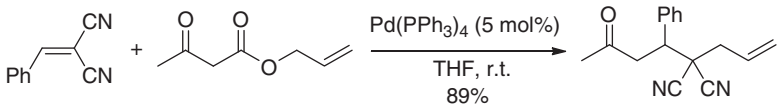
Two vicinal quaternary carbon centers could be installed by the reaction of stabilized carbon nucleophile with an allyl compound. For example, Xie et al. developed a successful strategy for the construction of two vicinal quaternary carbon centers with high diastereoselectivity and excellent enantioselectivity using a Pd-catalyzed AAA reaction with Trost's ligand **L12**.[47] This strategy has enabled the concise total syntheses of natural products hyperolactone C and (−)-biyouyanagin A from benzaldehyde in only six and seven steps with total yields of 20% and 8%, respectively (Scheme 7).[48]



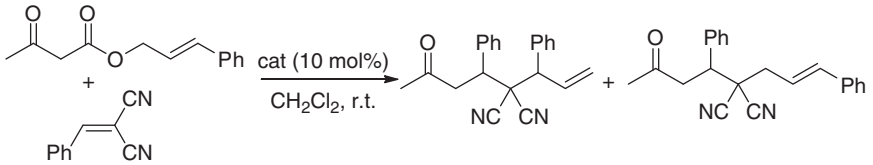
Scheme 7

New tandem reaction based on the *in-situ* generation of carbon nucleophile has been designed and developed, in which the nucleophile attacked π-allylpalladium complexes to form multiple bonds in one reaction. Yamamoto and coworkers reported the intermolecular β-acetonation-α-allylation of activated olefins with allyl acetoacetate proceeded through a tandem Michael addition

and allylic substitution in the presence of a catalytic amount of $Pd(PPh_3)_4$ (equation 23).[49] It should be noted that at least one CN group should be presented in activated olefins. The linear allylation products were given using a Pd catalyst whereas the branched allylation products were offered if Rh-catalyst was used (equation 24).[50]



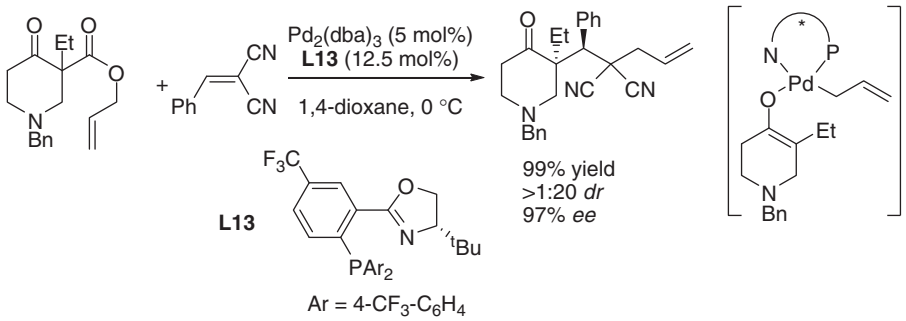
(23)



(24)

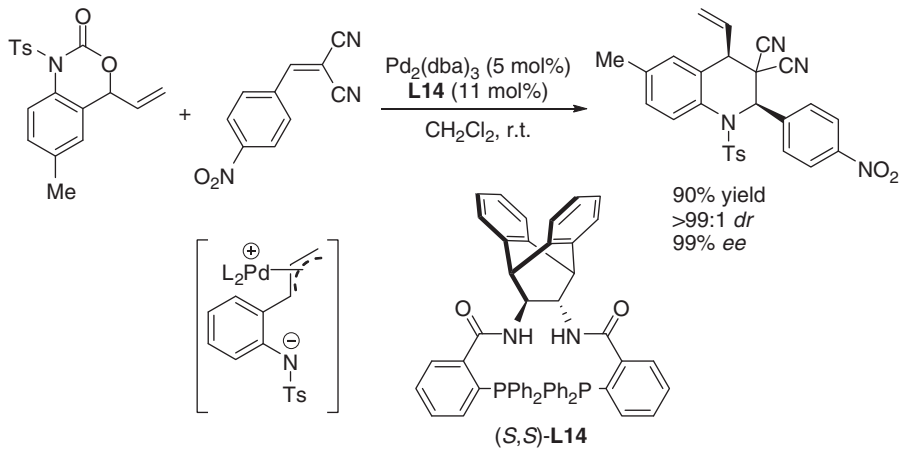
Cp*Ru(bpy)Cl	89%	< 5%
$Pd(PPh_3)_4$	< 5%	80%

Asymmetric version of the reaction was reported via decarboxylative addition of cyclic β-ketoesters to activated olefins. It allowed the formation of adjacent quaternary and tertiary carbon stereocenters with high enantioselectivity and diastereoselectivity.[51] The researchers proposed that the reaction proceeded through a chiral η^1-allyl,*O*-bound palladium enolate intermediate, which underwent an asymmetric addition to activated alkenes (equation 25).



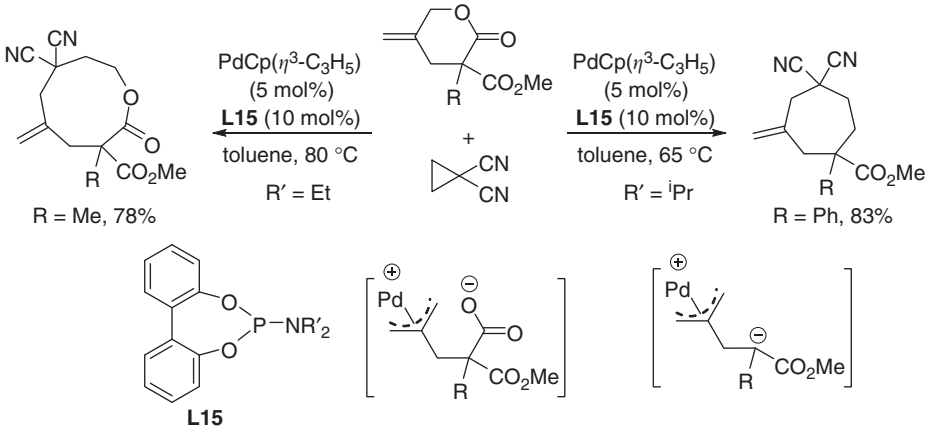
(25)

On the basis of the similar strategy, a palladium-catalyzed decarboxylation of benzoxazinanone followed by a cycloaddition with arylidene malononitriles was reported to generate highly substituted dihydroquinolines (equation 26).[52] A zwitterionic intermediate derived from vinylbenzoxazinone is proposed as the reactive species, which is equivalent to aza-*ortho*-xylylenes polarized by Pd metal. Both high enantioselectivity and diastereoselectivity are provided in the presence of the anthracenyl Trost ligand **L14**.



(26)

Shintani, Hayashi, and coworkers revealed that the palladium catalyst underwent oxidative addition with γ-methylidene-δ-valerolactones, giving rise to an amphiphilic π-allylpalladium carboxylate intermediate (equation 27).[53] When R is an aryl group, successive decarboxylation occurred to furnish 1,4-zwitterionic species as the aryl group can stabilize the resulting anionic charge on the adjacent carbon, which attacked 1,1-dicyanocyclopropane followed by a ring closure to give a seven-membered carbocycle. When R is an alkyl group, the decarboxylation is reluctant to take place, thus a direct nucleophilic attack of the carboxylate followed by ring closure led to a nine-membered lactone.

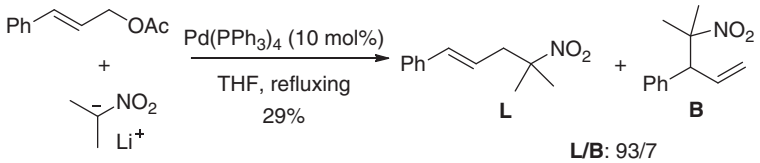


(27)

4.11.2.2 Nitroalkanes

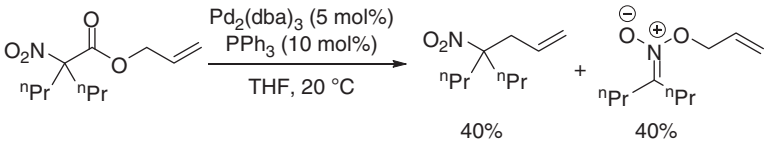
Nitro group containing compounds are valuable building blocks because of their convenient transformation into a wide variety of synthetically important compounds such as amines, carboxylic acids, aldehydes, and nitriles. The use of active methylene compounds such as α-nitro ketones, α-nitro esters, and α-nitro sulfones, which stabilized nitroenolates has been widely used in Tsuji–Trost type allylations.[54] This subsection will only focus on the use of simple nitroalkanes as nucleophiles.

The first reported primary nitroalkanes in *C*-allylation with cinnamyl acetate and 2-butenyl acetate catalyzed by $Pd(PPh_3)_4$ appeared in 1982.[55] Sterically demanding 2-nitropropane gave *C*-allylation product in only 29% due to the severe competing *O*-allylation (equation 28).[56]

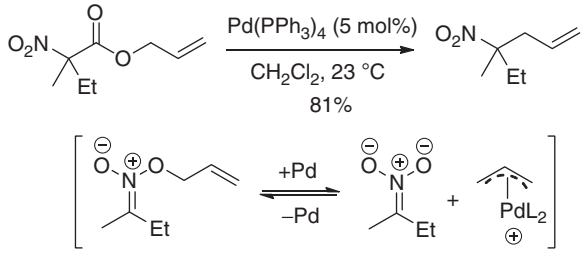


(28)

A Pd-catalyzed decarboxylative alkylation reaction of an allyl nitroacetate addressed the problem to obtain tertiary homoallylic nitro compound. Tsuji reported a single example of this reaction under mild conditions without external base. However, the reaction suffers a competing *O*-allylation, affording equal amounts of the isomeric *C*- and *O*-allylation products (equation 29).[57] By switching the catalyst to $Pd(PPh_3)_4$, Tunge found that *O*-allylation was efficiently suppressed and the *C*-allylated product was afforded in high yield (equation 30).[58] The researcher uncovered that the *C*-allylation was favored at a higher concentration of the reaction. The reason is attributed to the fact that a reversible *O*-allylation and high concentration of Pd catalyst enable *O*-allyl nitronate to reform the intermediate π-allyl complex, which then produces the *C*-allylated product.

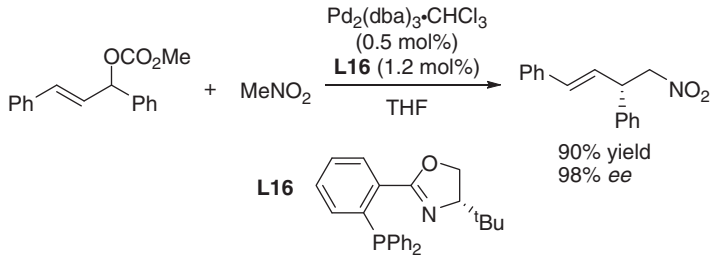


(29)



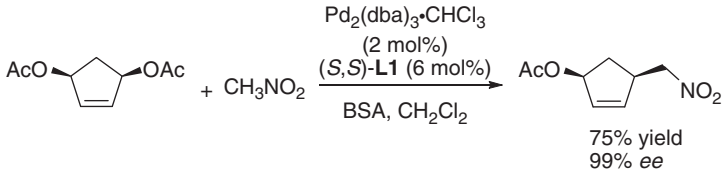
(30)

Enantioselective control was realized for the Pd-catalyzed alkylation reaction of nitroalkanes with allyl substrate in the presence of chiral ligand. In 1988, Genet and coworkers reported the asymmetric intramolecular allylation reaction of nitro compound using a Pd complex bearing a classical C_2 symmetry diphosphanes, and up to 70% *ee* was achieved.[59] An intermolecular allylic substitution with nitromethane gave an enantioselectivity of 98% as disclosed by Rieck and Helmchen using a Pd complex of phosphinoxazoline **L16** in 1995 (equation 31).[60] Hamada and coworkers achieved this allylation reaction with up to 98% *ee* using an aspartic acid-derived P-chirogenic diaminophosphine oxide ligand.[61] The resulting products were successfully applied to enantioselective synthesis of (*R*)-preclamol and (*R*)-baclofen.



(31)

Pd-catalyzed allylic alkylation reaction of nitroalkanes with cyclic allyl esters provided the monoalkylated product in near perfect *ee* under the effect of Trost's ligand (equation 32).[62] The product was converted into a known carbanucleoside intermediate of D-nucleosides. The same catalyst system also worked well for the allylic alkylation of nitroethane with acyclic 1,3-dimethyl allyl substrate, which formed two vicinal chiral centers with good diastereoselectivity and excellent *ee* (equation 33).[63] The reaction was intriguing that lowering the catalyst loading increased both diastereo- and enantio-selectivities.



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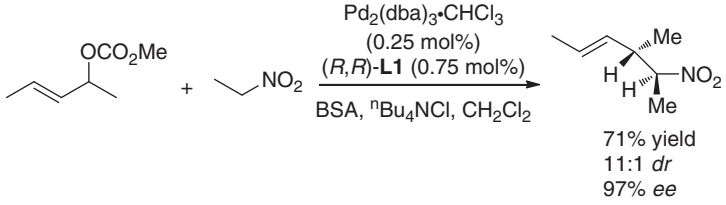
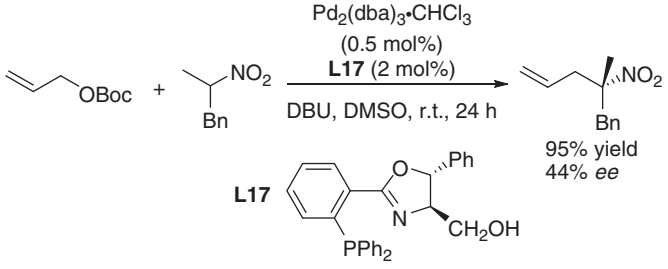


(33)

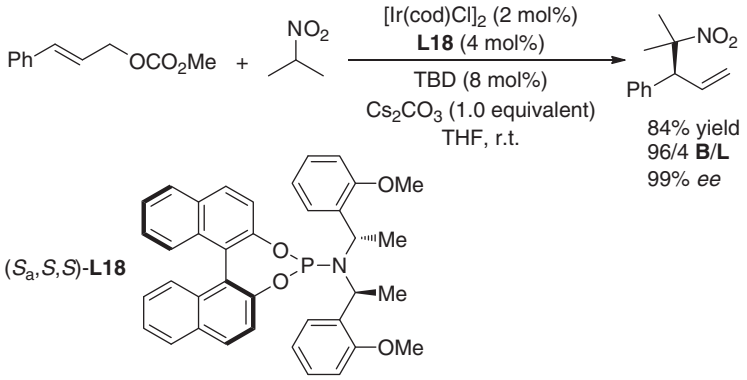
More recently, Shibasaki developed an improved procedure for allylic alkylation of bulky secondary nitroalkanes using a catalytic amount of external base (equation 34).[64] The critical issue of the reaction with high reactivity relied on the use of a strong base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the polar aprotic solvent DMSO. Asymmetric induction at the α-position of nitro functionality showed moderate selectivity with PHOX ligand **L14** containing a free OH group.



(34)

Dahnz and Helmchen reported on regio- and enantioselective Ir-catalyzed allylic alkylations of cinnamyl methyl carbonate with nitroalkanes as nucleophiles.[65] Up to 99% *ee* was achieved using catalysts prepared by *in situ* combining $[Ir(COD)Cl]_2$ with

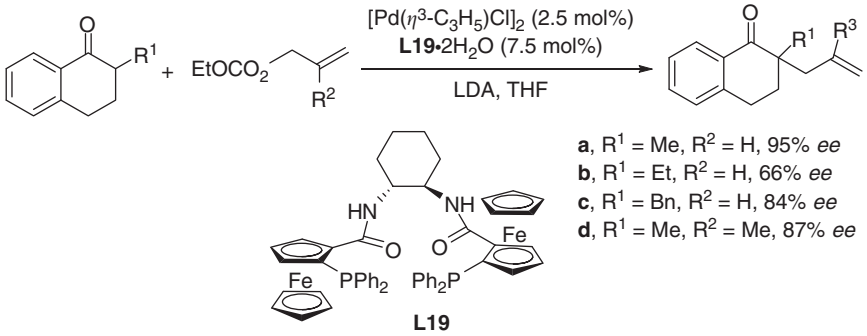
phosphorus amidites **L18** upon treatment with a base, TBD(1,5,7-triazabicyclo-[4.4.0]dec-5-ene) (equation 35). However, the protocol is not applicable to nitromethane.



(35)

4.11.2.3 Ketones and Aldehydes

Simple ketone enolates are an important class of nucleophiles in organic synthesis. Transition metal-catalyzed allylation of simple ketone is not successful under usual conditions for long time because of their nonstabilized character. The breakthrough came in 1999 when Trost and Schroeder reported asymmetric allylation of tetralone and cyclohexanone enolates with allyl substrates.[66] The allylation of 2-methyltetralone with allyl acetate reached 88% *ee* and 99% yield with their chiral pocket ligand. The base played a critical role in the reaction. Switching the base from lithium diisopropylamide (LDA) to Na and K base led to no reaction. Dai, Hou, and coworkers improved the enantioselectivities of the reaction to 95% using a ferrocene-based chiral ligand **19** (equation 36).[67] It is interesting to note that ligand **19** was easily crystallized with two water molecules, which afforded a higher *ee* value than the water-free ligand **19**. In addition to simple allyl reagent, 2-methyl allyl carbonate was also a suitable electrophile for the reaction.

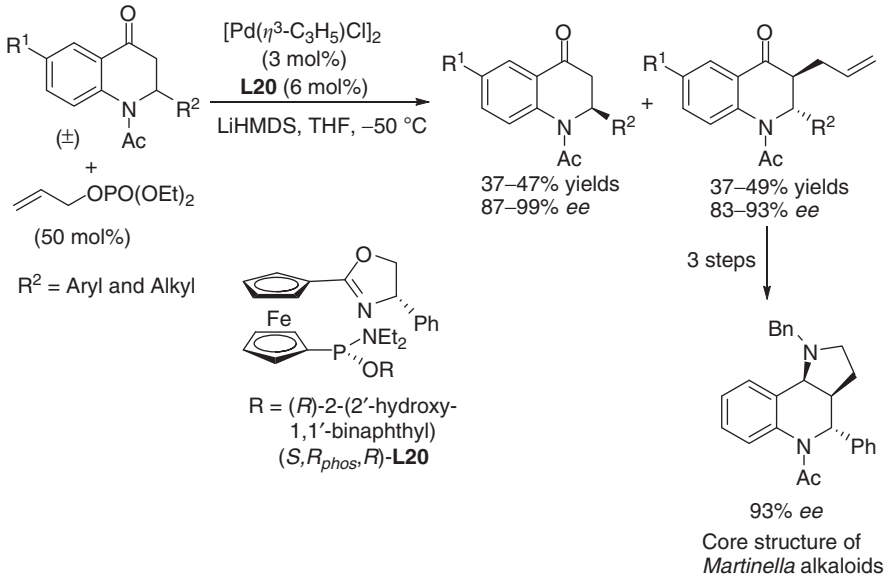


(36)

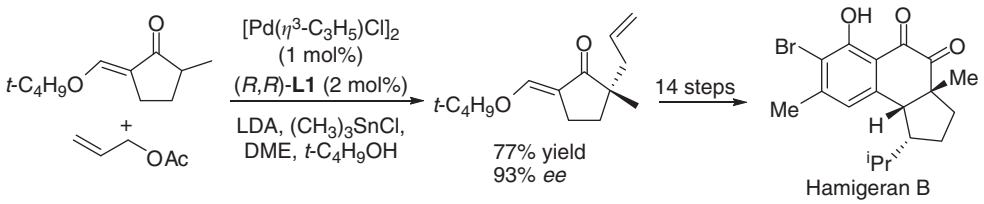
Hou and coworkers reported that kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones took place by Pd-catalyzed allylic alkylation reaction (Scheme 8).[68] The work represents the first example of kinetic resolution of a carbon nucleophile via Pd-catalyzed AAA reaction. In the presence of the SiocPhox ligand **L20**, both 2,3-disubstituted 2,3-dihydro-4-quinolones and the recovered substrates were obtained in high yields and *ee*'s with an *S*-factor of 44–145. Allylated product was easily converted into pyrrolo[3,2–c]quinoline without loss of optical activity through ozonolysis and reduction followed by reductive amination, which features the core structure of biologically active *Martinella* alkaloids.

Trost and coworkers have reported that the enolate derived from 2-methylcyclopentanone underwent asymmetric allylation in excellent *ee* (Scheme 9).[69] In this case, the addition of seven equivalents of *tert*-butyl alcohol improved enantioselectivity dramatically. This result demonstrated the importance of the presence of lithium alkoxides, which may affect the nature of the enolate clusters. For 14- steps, the allylated product was elaborated to hamigeran B in 10% overall yield.

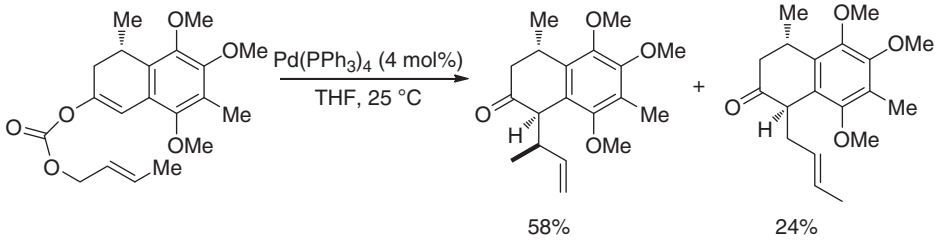
Decarboxylative alkylation of an allyl enol carbonates catalyzed by palladium–phosphine complexes is an alternative way to realize allylation of ketones or aldehydes. A very early example was disclosed by Tsuji and coworkers in 1983.[70] The reaction features good regioselectivity and mild reaction conditions. This method was applied as a crucial step in the total synthesis of colombiasin A by Nicolaou and coworkers. This decarboxylative alkylation preferred to form the desired branched allylation product as a single diastereomer over the corresponding linear product (equation 37).[71] Importantly, Nicolaou and coworkers failed to prepare the required ketone by conventional direct alkylation.



Scheme 8

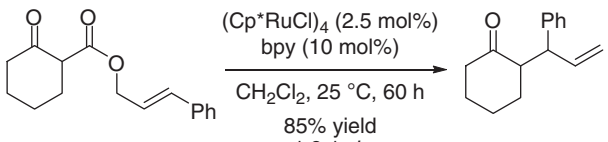


Scheme 9



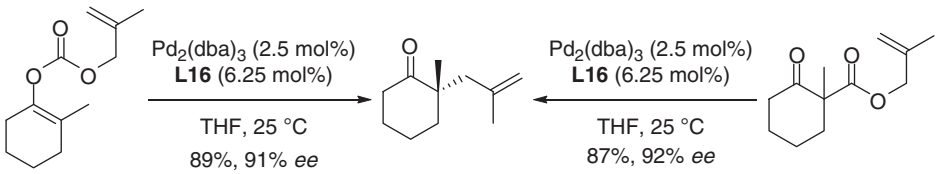
(37)

Compared with allyl enol carbonates, more easily synthesized and stable allyl β-ketoesters undergo decarboxylative alkylation to give allylated products. The early examples employed palladium catalysts to afford the product by nucleophilic attack at the least substituted allyl terminus.[72] Ruthenium complexes are also active catalysts for the decarboxylative alkylation of allyl β-ketoesters as reported by Junge and Burger (equation 38).[73] The reaction afforded branched product regioselectively due to the existence of a Ru-π-allyl species that preferentially occurred at carbon–carbon bond formation at the more hindered position. The reaction was applicable to a substrate with an α-substituent, although the resulting product suffered from a low *dr*.

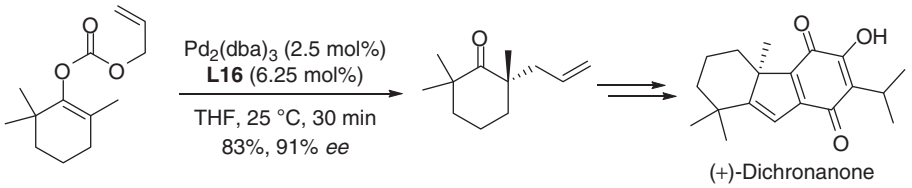


(38)

The asymmetric decarboxylative allylation of allyl enol carbonates was demonstrated firstly by Stoltz group in 2004 and Trost group later on.[74] These reactions provided a facial access to cycloalkanones with α-chiral quaternary carbon center, the widely useful chiral building blocks in organic synthesis, in highly enantioenriched form. In 2005, Stoltz and coworkers reported that decarboxylative allylation of allyl β-ketoesters also proceeded in a highly enantioselective manner.[75] The consistent stereoselectivities, whether starting from enol carbonate or allyl β-ketoester, suggested the possibility of a common reaction intermediate (equation 39). McFadden and Stoltz then applied this powerful method of the enantioselective construction of α-quaternary center of cyclic ketone as a key step in the total synthesis of (+)-dichronanone (Scheme 10).[76]

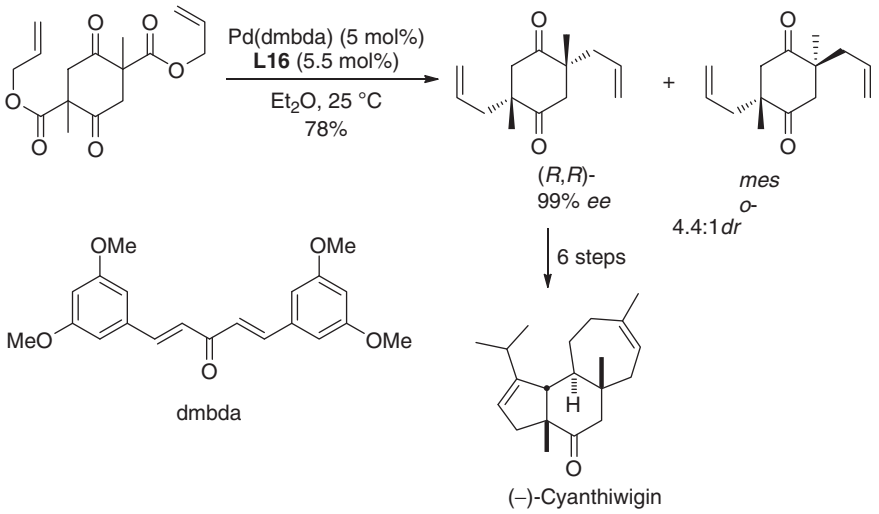


(39)



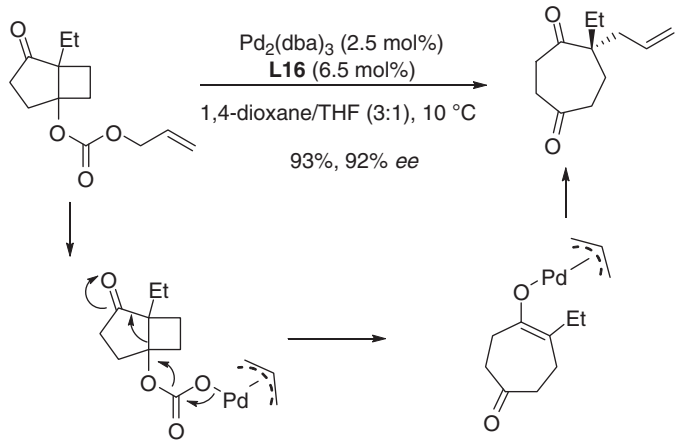
Scheme 10

A 1:1 mixture of diastereomeric diesters underwent a double decarboxylative allylation to afford the desired diastereomer of the enantioenriched ketone (dr = 4.4:1) in exceptional enantioselectivity (Scheme 11).[77] The product was elaborated to the natural product with two chiral quaternary carbon centers, (−)-cyanthiwigin, in six steps.



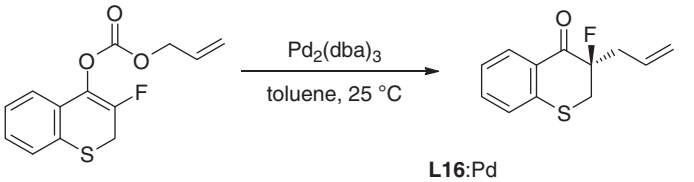
Scheme 11

The bicyclo[3.2.0]heptane-2-one derivative was formed through an asymmetric ring expanding allylation reaction under palladium catalysis (equation 40).[78] The reaction may involve anionization to generate the alkoxide ion, which underwent a retro-aldol reaction to afford an enolate and allylation. This method allows the preparation of enantioenriched substituted cyclic 1,4-diketones derivatives.



(40)

Fluorinated enol carbonates underwent the asymmetric decarboxylative allylation as reported by Paquin and coworkers (equation 41).[79] An interesting feature of the reaction is that the *ee*'s of the product fluoroketones are highly dependent on the ligand-to-palladium ratio. For example, a 1.25:1 of ligand/Pd ratio with a ligand excess led to the product in moderate *ee*. Alternatively, using an L/Pd ratio of 1:4 furnished the product with high enantioselectivity. In contrast, similar phenomena did not occur in the decarboxylative allylation of fluorinated β-ketoesters and an alkyl-substituted enol carbonate, or allylation of a fluorinated silyl enol ether. Although the reason is unclear, these results demonstrated that different fluorinated enolate precursors had different selectivities.

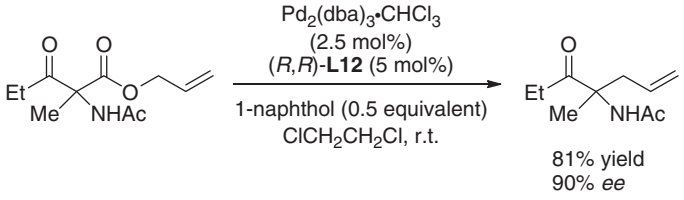


L16:Pd

1:4 92% *ee*; 90% yield
1.25:1 42% *ee*; 93% yield

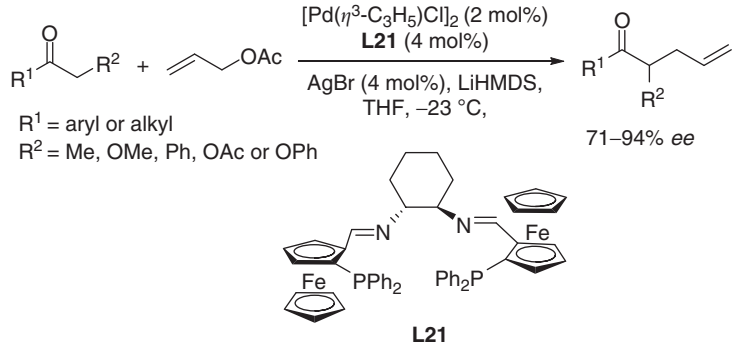
(41)

The decarboxylative allylation of acyclic β-ketoesters usually suffers from low enantioselectivity due to a mixture of enolates with different geometries generated. Placing an appropriate functional group in the substrate constitutes a solution. Murakami and coworkers reported that decarboxylative allylation of acyclic α-acetamido-β-ketoester resulted in enantioenriched γ,δ-unsaturated α-aminoketone in the presence of a palladium complex modified with a chiral phosphine ligand (equation 42).[80] In contrast, no asymmetric induction was observed with the α-alkyl ketoesters as substrates. The results highlighted the importance of the presence of acetamido group for controlling the stereochemistry. In addition, the absence of 1-naphthol additive led to a much lower *ee* (51%).



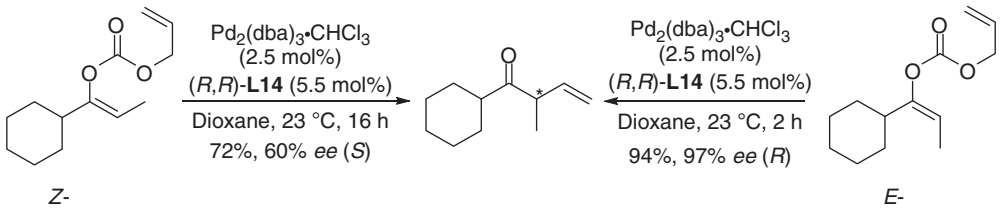
(42)

The AAA reaction of simple acyclic ketones with simple allyl acetate was developed for the first time with a wide range of substrate scope by Hou and coworkers using a chiral Pd catalyst.[81] A high *ee* was provided when the alkoxy group was placed in the α-position of the carbonyl group (equation 43). The use of AgBr as additive improved both reactivity and enantioselectivity of the reaction. The enolate form of ketones dramatically affected the enantioselectivity of the reaction. The alkoxy group in the substrate may favor the formation of the defined enolate geometry.

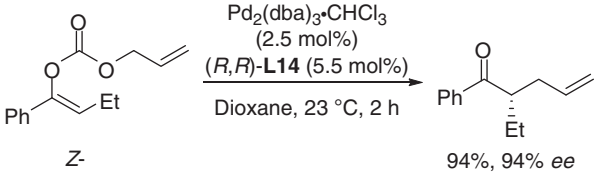


(43)

The similar effect of the enolate geometry on the allylation reaction was observed in decarboxylative allylation of allyl enol carbonate by Trost et al.[82] They found that the preformed *E*-enol carbonate was more reactive than the *Z*-analog under the same conditions (equation 44). The former also gave much higher *ee* and opposite enantiomer compared with that for Z-enol carbonate. These results indicated that the *E*-isomer was matched with the catalyst whereas the *Z*-isomer was mismatched. However, the phenomena were only observed for carbonates derived from dialkyl ketones. Z-enol carbonates derived from a phenyl ketone are excellent substrates for asymmetric decarboxylative allylation reaction (equation 45).

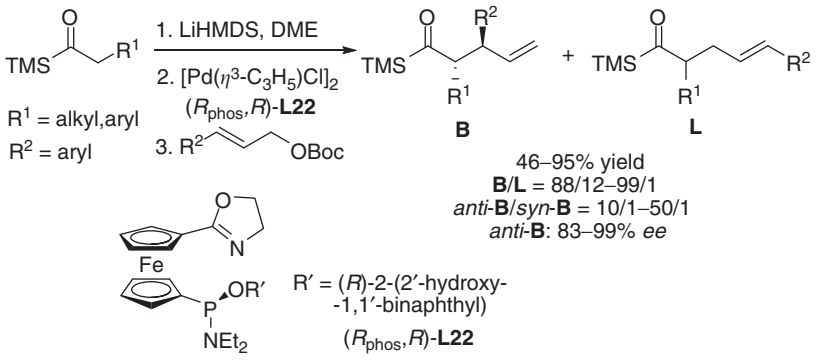


(44)

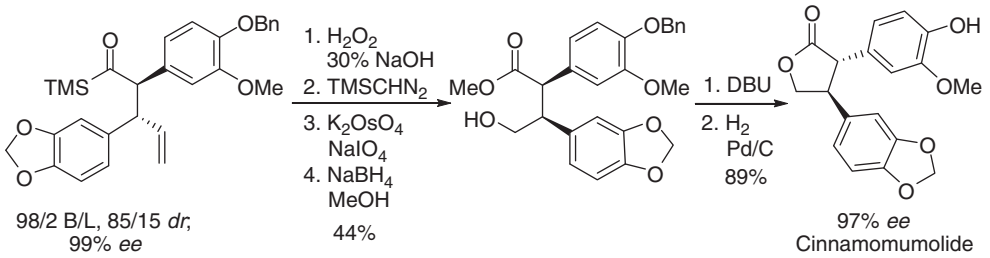


(45)

The reaction of simple ketone enolates and monosubstituted allyl substrates can generate two vicinal chiral centers, in which not only the enantioselectivity but also the regio- as well as diastereoselectivities should be controlled. Hou and coworkers realized this challenging task using a Pd/SiocPhoxcatalyst.[83] The products were formed in high yields with high regio-, diastereo-, and enantioselectivities. The presence of LiCl or CuCl favored the formation of branched products whereas CuI gave linear products predominantly. A drawback of the reaction was the diastereoselectivity. Hou and coworkers developed acylsilanes as a new 'hard' carbon nucleophile precursor for such reaction (equation 46).[84] In the presence of the same SiocPhox ligand, high regio-, diastereo-, and enantioselectivities were achieved. The resulting product was easily converted into the corresponding ester, alcohol, and ketone with good retention of stereoselectivity. It highlights the advantage of acylsilanes for further transformation. The usefulness of the protocol has also been demonstrated by the enantioselective synthesis of the natural product cinnamomumolide (Scheme 12).

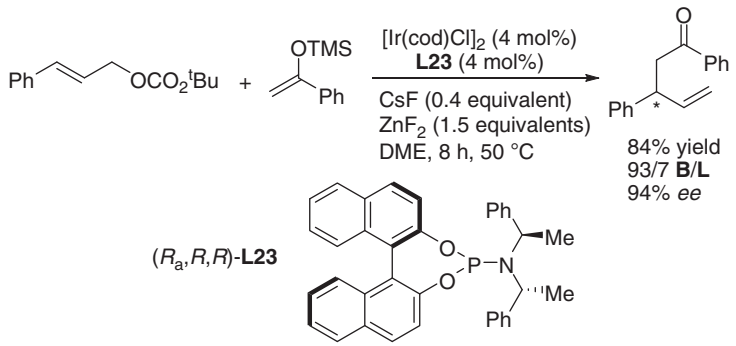


(46)



Scheme 12

Silyl enol ethers and enamines, an equivalent of simple ketone, reacted with linear allylic carbonates to form β-branched, γ,δ-unsaturated ketones in the presence of iridium-phosphoramidite catalysts in high yields, branched selectivity, and enantioselectivity for a range of cinnamyl and alkyl-substituted allylic carbonates (equation 47).[85] The enamines derived from many kinds of aliphatic ketones also reacted in high yields and selectivity (equation 48).[86]



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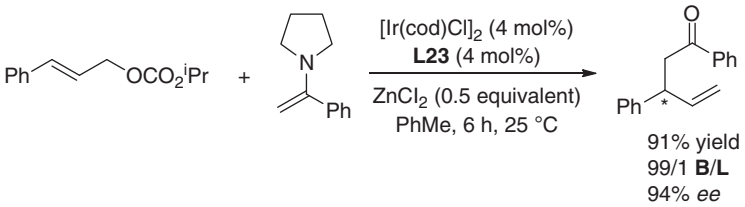
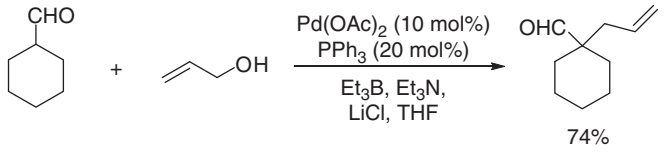


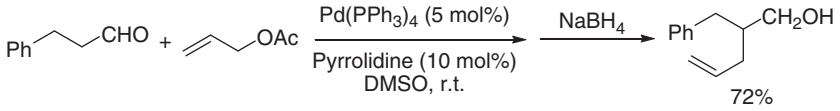
(48)

The conventional alkylation of aldehydes usually relies on the stoichiometric use of preactivated aldehydes such as their metal enolates, silyl enol ethers, enol carbonates, or enamines. Thus, the catalytic α-allylic alkylation of nonstabilized aldehydes is particularly challenging due to competing side reaction, such as Aldol condensation, Cannizzaro, and Tishchenko reactions, and *O*-alkylations. There are some intriguing solutions for the catalytic intermolecular α-allylic alkylation of simple aldehydes. Tamaru and coworkers revealed that the α-allylic alkylation of aldehydes with allyl alcohol was feasible in the presence of a catalytic amount of palladium and a stoichiometric amount of Et_3B, Et_3N, and LiCl (equation 49).[87]



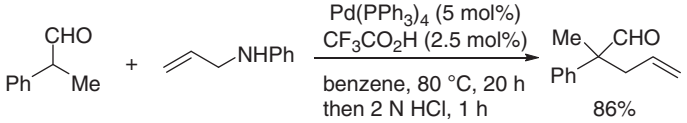
(49)

Ibrahem and Córdova disclosed a novel strategy of one-pot combination of enamine- and transition metal catalysis for direct intermolecular α-allylic alkylation of aldehydes (equation 50).[88] The reaction involves the attack of enamine intermediates generated *in situ* to catalytically formed electrophilic palladium π-allyl complex. Obviously, the reaction demonstrates that the intermolecular allylation is much faster than the self-aldol reaction of aldehyde catalyzed by the secondary amine used in the reaction. The researchers also showed the use of optically active pyrrolidine derivatives or (*S*)-proline instead of pyrrolidine led to α-allylic alkylated alcohol with high enantioselectivity but in moderate yields.



(50)

In 1985, Murahashi and coworkers reported a Pd(0)-catalyzed direct α-allylation of aldehydes using secondary allylamine as the allylating reagent (equation 51).[89] The presence of catalytic amount of trifluoroacetic acid as a cocatalyst was critical for the reaction. The reaction involved oxidative addition of Pd(0) species to allyl enammonium salt generated *in situ* from acid-catalyzed condensation of allylamine with aldehyde. π-Allylpalladium complex and enamine thus formed underwent nucleophilic substitution reaction. The removal of the Pd(0) species and a proton gave the imine product, which was hydrolyzed to furnish γ,δ-unsaturated aldehyde. In 2007, an asymmetric version of the reaction was revealed by Mukherjee and List, in which a chiral phosphoric acid was used as the cocatalyst.[90] In 2011, the same group demonstrated direct asymmetric α-allylation of aldehyde with simple allylic alcohols (equation 52).[91] A drawback of the reaction was narrow substrate scope and only α-branched aldehydes may be applied.



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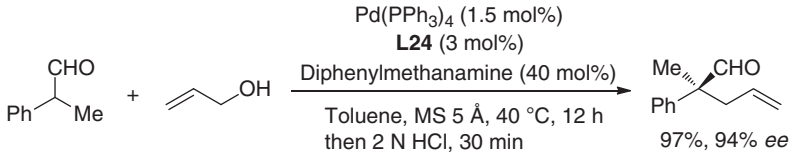
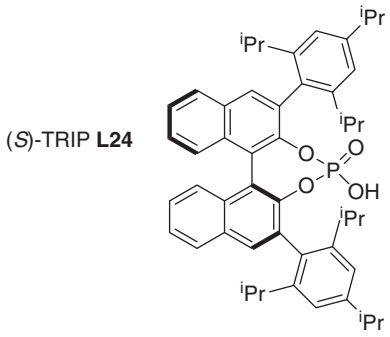
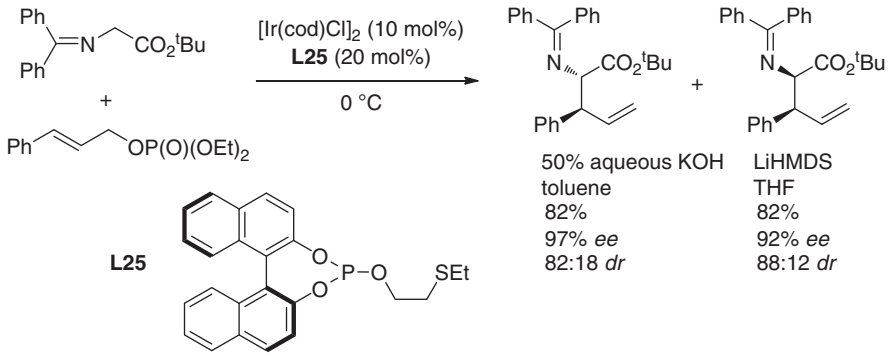




(52)

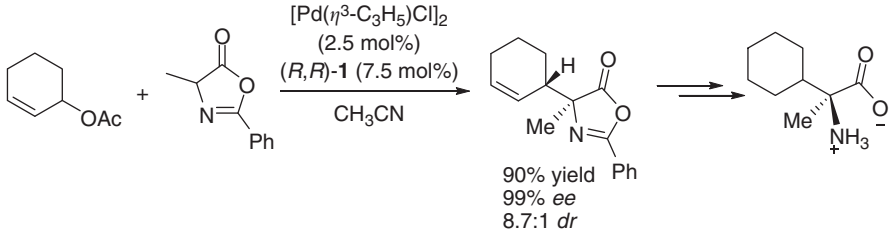
4.11.2.4 Carboxylic Acid Derivatives

Imino esters are useful nucleophiles in organic synthesis because they are one of the most important precursors of the relevant α-amino acids. Transition metal-catalyzed allylic alkylation reaction of imino esters with allyl substrates represents a straightforward way for the catalytic asymmetric synthesis of substituted α-aminoacids. The palladium catalyst was firstly used for such a reaction, but these catalysts usually did not give ideal stereoselectivity.[92] Iridium complexes of 1,1′-bi-2-naphthol (BINOL)-derived phosphite **L25** containing a thioether substituent catalyzed the alkylation of cinnamyl phosphates and a glycine nucleophile (equation 53).[93] The switchable diastereoselectivity was realized by varying the solvent and base. Both *trans* and *cis* diastereomers were formed in excellent *ee*.



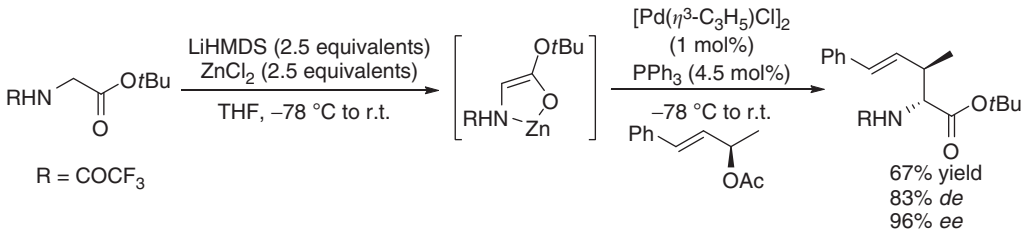
(53)

Azlactone, a readily available precursor of amino acid, underwent an allylation reaction with allyl substrate in the presence of a palladium catalyst. With the Trost ligand **L1**, a 90% yield of alkylated product with 8.7:1 *dr* and 99% *ee* of the major diastereomer was obtained when the reaction was carried out in acetonitrile (Scheme 13).[94] The allylated product was facially converted into quaternary amino acid without racemization. This reaction offered a successful route for catalytic asymmetric synthesis of amino acids. When cinnamyl carbonate was used as an allyl electrophile, the palladium catalyst only gave a linear product. The use of an Mo-catalyst led to the branched product with a high level of regioselectivity as disclosed by Trost and Dogra.[95]



Scheme 13

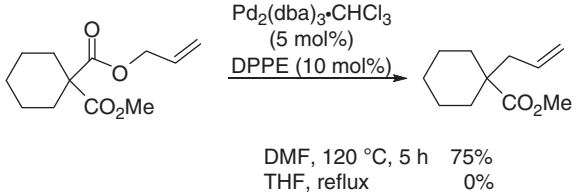
Chelated enolate of aminoacid ester developed by Kazmaier and Zumpe is an efficient nucleophile in palladium-catalyzed allylic substitutions.[96] The researchers suggested the chelation enhanced thermal stability of these enolates without negative influence on their reactivity. The fixed geometry of the enolates favored their allylic alkylation to proceed in a stereoselective manner, giving high yields and excellent stereoselectivities in allylic alkylation. Chiral allylic carbonates provided the corresponding substituted amino acids in optically pure forms (equation 54). A catalytic asymmetric version was developed with diastereomeric ratios of up to 95:5 and *ee*'s of up to 95% by collaboration of Helmchen and Kazmaier groups.[97]



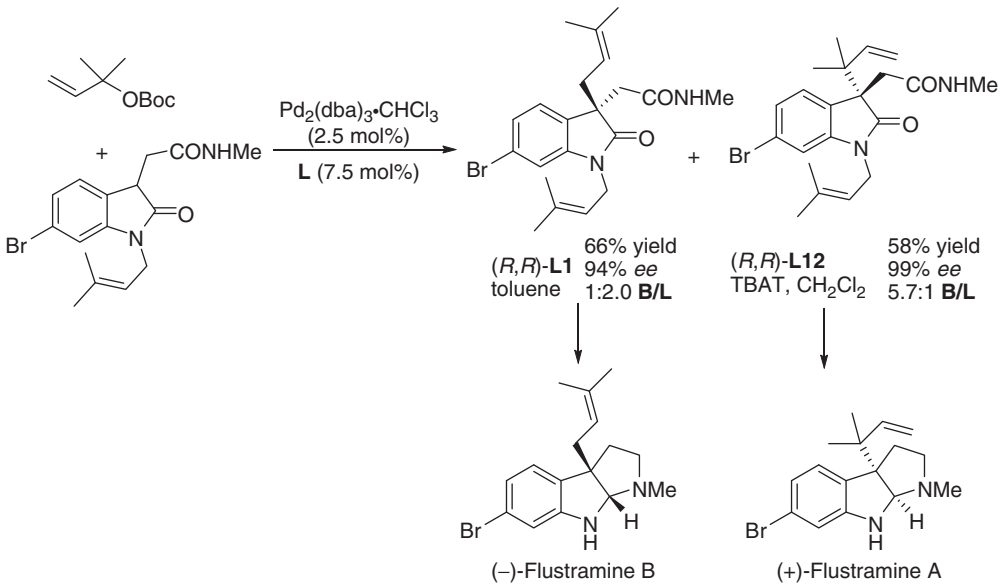
(54)

The oxindoles are valuable building blocks for alkaloid synthesis. Trost and Frederiksen initially reported that only 3-aryl oxindoles underwent allylic alkylation with simple allyl substrate to provide 3-alkyl-3-aryl oxindoles in high yield and enantioselectivity using a chiral palladium catalyst.[98] The protocol was not suitable for 3-alkyl oxindoles, which gave moderate enantioselectivity. This issue was addressed with chiral molybdenum catalyst by Trost and Zhang.[99] The quaternary stereocenter was generated at a prochiral carbon of 3-alkyl oxindoles in excellent enantioselectivity. The Mo-catalyzed AAA reaction involves nucleophile precoordinating to the metal followed by reductive elimination. The intimate interaction between the nucleophile and the chiral metal catalyst in the molybdenum system may result in the control of quaternary stereocenters. Very recently, Trost and coworkers disclosed that 3-alkyl oxindoles reacted smoothly with prenyl substrate to afford either branched or linear product selectively (Scheme 14).[100] The choice of ligand, solvent, and halide additive played a crucial role in the control of regioselectivity. The resulting prenylated products were transformed into *ent*-flustramines A and B.

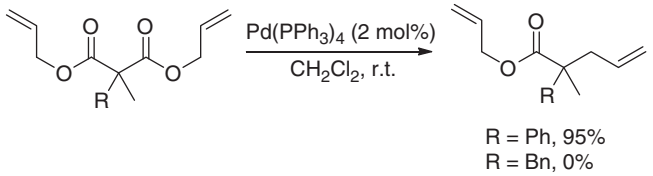
The allylic alkylation reaction of simple carboxylic acid derivatives by transition metal catalysis is particularly difficult due to the lower acidity of hydrogen atom at α-position of carboxylic acid group. The even less stabilized nature of carbanions derived from carboxylic acid derivatives constitutes another obstacle. The decarboxylative allylation of 1-allyl-1-methylmalonate is an indirect approach to the allylated product of ester as reported by Tsuji and coworkers in 1987 (equation 55).[57] The 1-allyl-1′-methylmalonate, in contrast to an allyl α-keto carboxylate, is less reactive and no reaction took place in boiling THF. Severe reaction conditions (120 °C in DMF) resulted in moderate yields. This may be attributed to the unstability of the α-ester carbanion generated by decarboxylation. Ohta and coworkers disclosed the decarboxylative allylation of α-aryl malonic acid derivatives occurred readily at room temperature, whereas no reaction took place with 1,1-diallyl 2,2-dialkylmalonates under the same conditions (equation 56).[101] These results also demonstrated that benzylic enolate generated by decarboxylation was well stabilized, which facilitated decarboxylation.



(55)

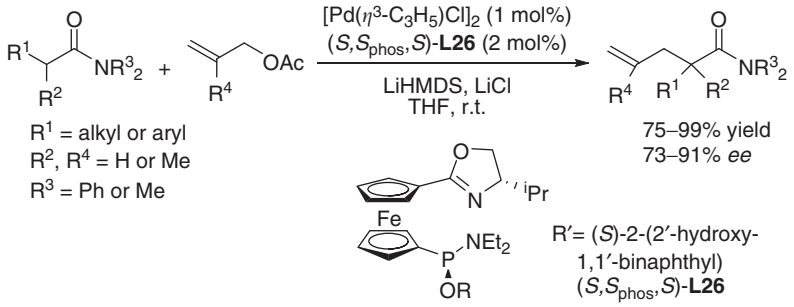


Scheme 14



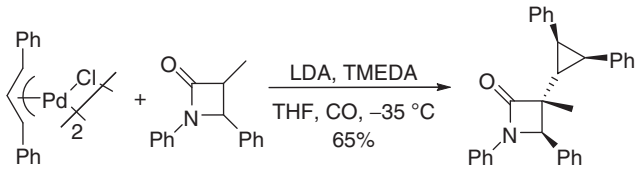
(56)

The direct AAA reaction of simple carboxylic acid derivatives is firstly reported by the group of Hou.[102] The acyclic amides, general carboxylic acid derivatives, were subjected to the reaction with allyl acetates under the effect of a SiocPhox ligand (equation 57). High yields of products with high enantioselectivities were obtained. The nature of the substituents on the nitrogen atom of the amide has a critical effect on the reactivity and stereoselectivity of the reaction. The best results were afforded when *N*,*N*-diphenyl amides were the substrates. Density functional theory calculations reveal that the substituent influences both the stability as well as the reactivity of the carbanion formed during the reaction.



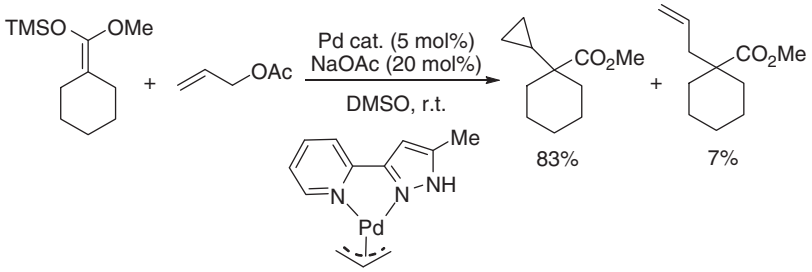
(57)

Ester enolate could attack the central carbon atom of a π-allylpalladium complex to form a cyclopropane as firstly reported by the Hegedus group in 1980.[16] Hoffmann and coworkers showed cyclopropanation of the deprotonated sterically hindered ester, ketone, sulfone, acid amide, and β-lactam with (π-phenylallyl)palladium complex occurred readily in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (equation 58).[103] However, the alkyl-substituted (π-ally1) palladium complexes provided no cyclopropane under identical conditions. These results highlighted that the phenyl substituent facilitated cyclopropanation although the reason was unclear. Hoffmann and coworkers also isolated and characterized the palladacyclobutane derived from the reaction of (π-1,3-diphenylallyl)palladium with deprotonated isobutyronitrile.[104,105] The palladacyclobutane readily proceeded reductive elimination to afford the cyclopropane in the presence of CO, which demonstrates unequivocally the direct attack of the bulky enolate on the central carbon atom of a π-allylpalladium complex.



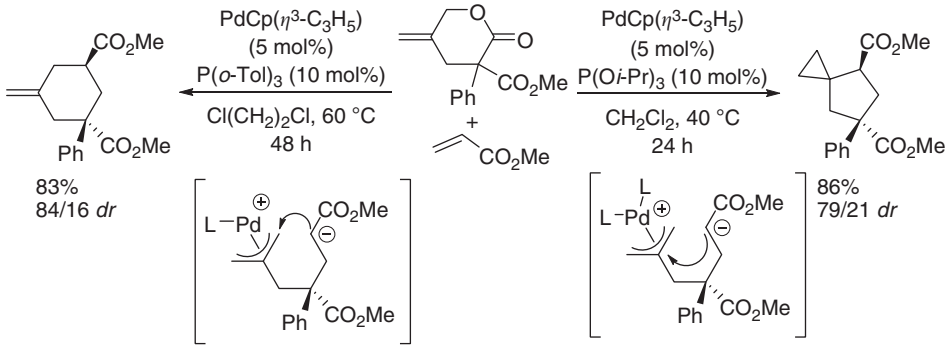
(58)

Musco, Santi, and coworkers reported the first example of Pd(0)-phosphine complex-catalyzed cyclopropanation of ketene silyl acetals with allylic acetates though the ratio of cyclopropane/allylated product was low.[106] In 1998, Satake and Nakata showed that the reaction favored the formation of cyclopropane using a π-allylpalladium-pyridinylimidazole complex (equation 59).[107a] The active catalyst was a neutral complex whereas the cationic complexes gave trace amounts of cyclopropane, which may be explained by the fact that the neutral complex prevented ligand dissociation even in DMSO and allowed facial cyclopropanation. DMSO, which might accelerate the reaction in the oxidative addition and reductive elimination steps, was critical for the reaction as no reaction proceeded in other solvents. One year later, the Satake group uncovered an asymmetric version of the reaction albeit only moderate enantioselectivities were obtained.[107b]



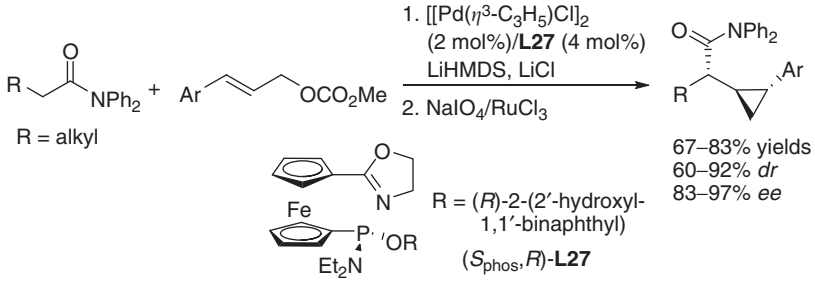
(59)

Hayashi and coworkers showed that the *in-situ*-generated ester enolate by palladium-catalyzed decarboxylative of γ-methylidene-δ-valerolactones underwent an intramolecular cyclopropanation using phosphite ligands [$P(OMe)_3$, $P(O^iPr)_3$] with high stereoselectivity (**Scheme 15**).[108] Allyic alkylation product was formed in the presence of 5 mol% $CpPd(\eta^3\text{-}C_3H_5)$ and bulky phosphine ligands such as $P(o\text{-Tol})_3$. The researcher proposed that different reaction intermediates are responsible for the formation of different products. The $Pd(\eta^3\text{-allyl})P(O^iPr)_3$ species mainly favor the ring closure through the central attack, whereas the $Pd(\eta^3\text{-allyl})P(o\text{-Tol})_3$ species favor the six-membered ring formation by the terminal attack.[109]



Scheme 15

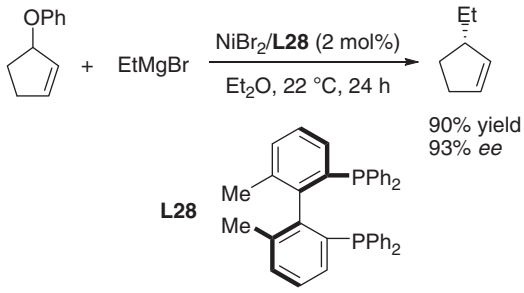
The Hou group made a breakthrough in the asymmetric cyclopropanation reaction by palladium catalysis. The reaction of acyclic amides and monosubstituted allyl substrates in the presence of Pd/chiral ligand SIOCPhox afforded cyclopropanes in high yields and high diastereo- and enantioselectivities (equation 60).[110] The introduction of LiCl as an additive greatly improved the selectivity. Three stereogenic centers were formed in one process from two easily accessible starting materials.



(60)

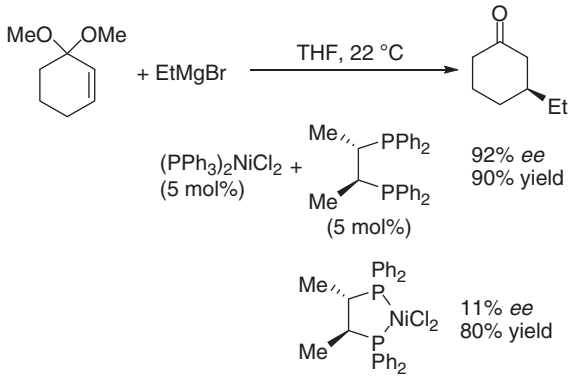
4.11.2.5 Organometallic Reagent

Transition metal-catalyzed allylation reaction of organometallic reagents derived from the main-group elements such as Grignard reagents and organolithium or organozinc compounds have also been well investigated. In 1977, Grignard reagents were reported to react with allylic alcohols when nickel–phosphine complexes were used as the catalyst precursor.[111] Although Consiglio and Indolese showed that the asymmetric addition of EtMgBr to cyclic allylic phenyl ether occurred with 93% *ee* and 90% yield in the presence of a chiral Ni catalyst with **L28** as the chiral ligand (equation 61).[112] Variation of catalyst structures revealed that the enantioselectivity was mainly affected by steric rather than electronic factors.



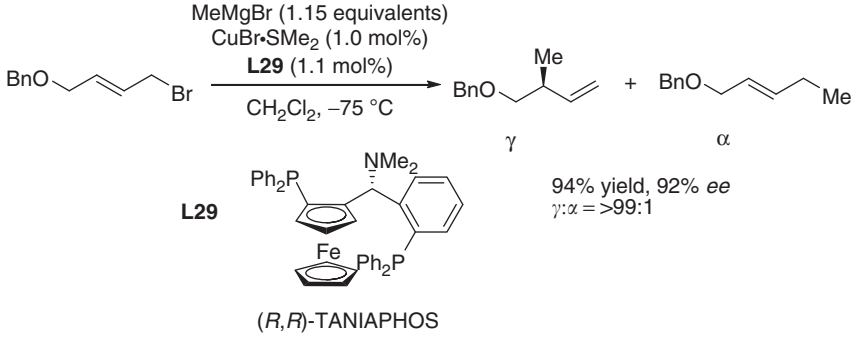
(61)

On the basis of previous reports of Ni-catalyzed addition of Grignard reagents to allylic acetals,[113] Hoveyda and coworkers reported an Ni-catalyzed enantioselective addition of EtMgCl to cyclohexenyl acetal. A presynthesized catalyst (*S*,*S*)-chiraphos/$NiCl_2$ gave product in only 11% *ee* and 80% yield, whereas the use of *in-situ*-generated catalyst led to 92% *ee* (90% yield) (equation 62).[114]



(62)

Copper catalysts allow hard organometallic nucleophiles such as organolithium, Grignard, and organozinc reagents to attack regioselectively at the γ-position of allyl substrate.[115] This protocol incorporates a simple alkyl fragment at the γ-position and provides branched chiral products containing a terminal olefin functionality. The first chiral copper(I) complex-catalyzed asymmetric cross-coupling reaction of Grignard reagents with allylic substrates was reported by Bäckvall and van Koten in 1995 with moderate enantioselection.[116] Since then, many chiral ligands were developed for this reaction and excellent enantio- and regioselectivities were realized.[117] For example, the TaniaPhos-based catalyst is particularly effective in the Cu-catalyzed AAA reaction of linear aliphatic allylic bromides, affording almost exclusively γ-products with 92% enantioselectivity (equation 63).[118] Allylic substitution product was conveniently transformed into bifunctional chiral building blocks such as monoprotected diol by hydroboration–oxidation reaction and β-hydroxyketone by oxidation of alkene group (**Scheme 16**).



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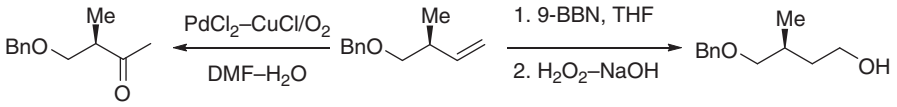
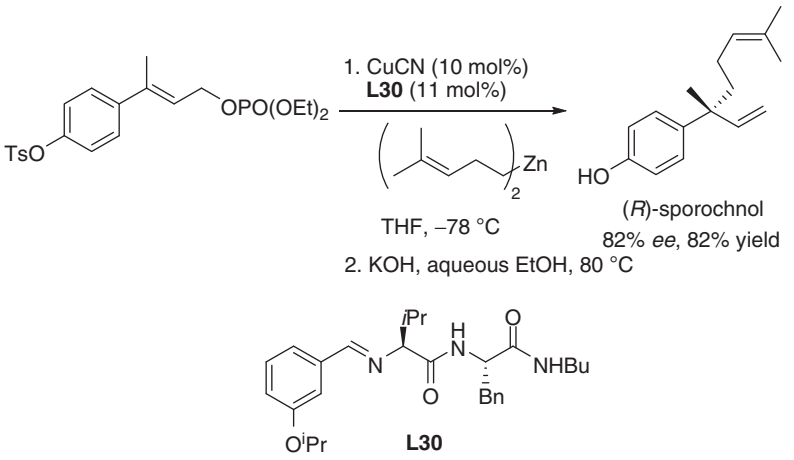


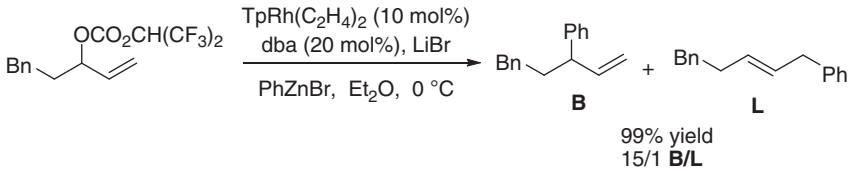
Scheme 16

Dübner and Knochel made a breakthrough using dialkylzinc as an alkyl source for copper-catalyzed asymmetric allylic substitutions in 1999, although a high ratio of ligand to copper, at very low temperatures, and the presence of bulky alkyl groups on zinc is necessary to attain a high enantioselectivity.[119] The reaction of dialkylzinc reagents with allyl substrates under catalysis of copper can form a quaternary carbon as reported by Hoveyda and coworkers (equation 64).[120] The use of a pyridinyl peptide ligand **L30** allowed the excellent enantiofacial control. The allylic alkylation was utilized for the enantioselective synthesis of (*R*)-sporochnol, a fish deterrent from the Caribbean marine alga *Sporochnus bolleanus*. Hoveyda and Murphy then extended substrate scope to α,β-unsaturated carbonyl bearing a primary γ-phosphate, which was treated with alkylzincs to provide synthetically useful and versatile α-alkyl-β,γ-unsaturated carbonyls in the optically enriched form.[121]



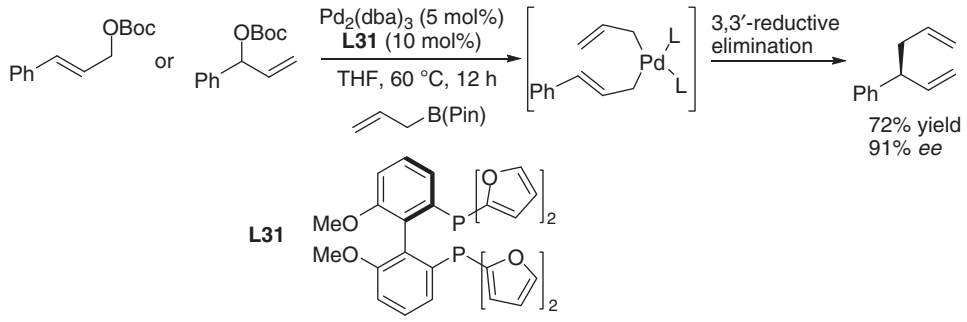
(64)

Arylzinc bromides are reported to react with acyclic branched allylic alcohol derivatives with rhodium catalyst to afford regioselectively the branched allylated product (equation 65).[122] The addition of lithium bromide was crucial for obtaining optimal regiospecificity. The leaving groups affected the regioselectivity dramatically: the traditional leaving groups, such as methyl carbonate, favored the formation of the linear allylic alkylation adducts, the fluorinated leaving groups was beneficial for the specificity. When the primary allylic carbonate was subject to the reaction with arylzinc under the same reaction conditions, the linear allylic alkylation product was furnished as the major isomer. Alexakis and coworkers reported the AAA reactions of arylzinc reagents with primary allylic carbonates in the presence of a chiral iridium phosphoramidite catalyst.[123] The arylzinc reagents were generated by the reaction of the corresponding aryl Grignard reagent and $ZnBr_2$. Although the excellent enantiocontrol was obtained, the reaction still suffered from poor regioselectivity, typically approximately 1:1.



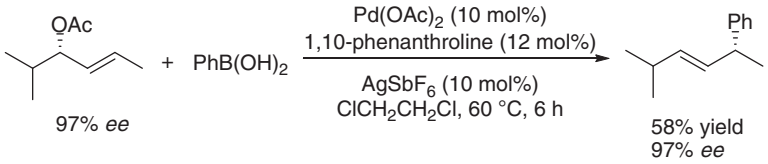
(65)

Pd-catalyzed coupling reaction of organoboron compound with allylic phenoxide proceeded via a (π-allyl)palladium(II) intermediate to afford a linear product.[124] Morken and coworkers reported a highly regio- and enantioselective allyl–allyl coupling of allylic carbonate and allylB(Pin).[125] The regioselectivity of the reaction is rationalized through a 3,3′ reductive elimination of bis(allyl)Pd complexes. The bite angle of the ligand impacted greatly on the regioselectivity. Small-bite-angle ligands favored the branched substitution product. The reaction was extended for the asymmetric construction of hindered quaternary carbon centers (equation 66).[126]



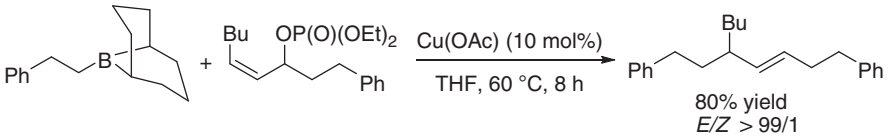
(66)

Sawamura and coworkers reported that the arylboronic acids reacted regioselectively and stereospecifically at the γ-position of allylic acetates on using the cationic palladium(II) catalyst (equation 67).[127] The regioselectivity was rationalized by the regioselective C–C bond insertion into the ary-Pd bond with the assistance of intramolecular coordination of the carbonyl oxygen of the acetoxy group to the cationic Pd center.



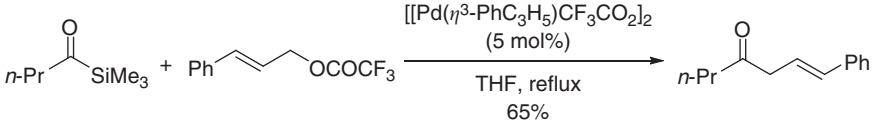
(67)

γ-Selectivity was also observed in the Cu-catalyzed reaction of alkylboron compound (alkyl-9-BBN) with (*Z*)-acyclicallyl phosphate (equation 68).[128] The mechanisms involved transmetallation between a trialkyl(alkoxo)borate and a copper(I) salt to form an alkylcopper(I) species. Later, Hayashi and coworkers reported an asymmetric allylic substitution of allyl phosphates and aryl- and alkenylboronates with a chiral copper/*N*-heterocyclic carbene(NHC)catalyst,[129] whereas Jung and Hoveyda used allenylboronic acid pinacolester as a nucleophile in a copper-catalyzed site and enantioselective allylic substitution.[130]



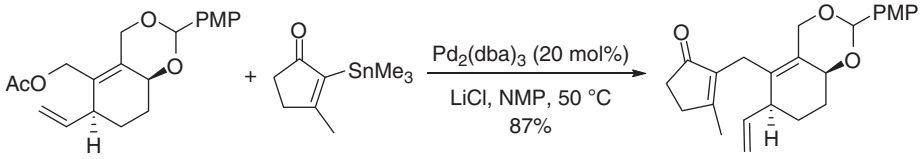
(68)

Acylsilanes reacted with allylic trifluoroacetate in the presence of a catalytic amount of $[Pd(\eta^3\text{-}C_6H_5CH{=}CHCH_2)(CF_3COO)]_2$ to give selectively β,γ-unsaturated ketones (equation 69).[131] The leaving group of the allylic esters played a crucial role in the reaction as no reaction took place with allyl acetates and trichloroacetates.



(69)

Alkenylstannane underwent a palladium-catalyzed Stille coupling reaction with allylic acetate to give the product in 87% yield, which was an intermediate toward the synthesis of guanacastepene (equation 70).[132]

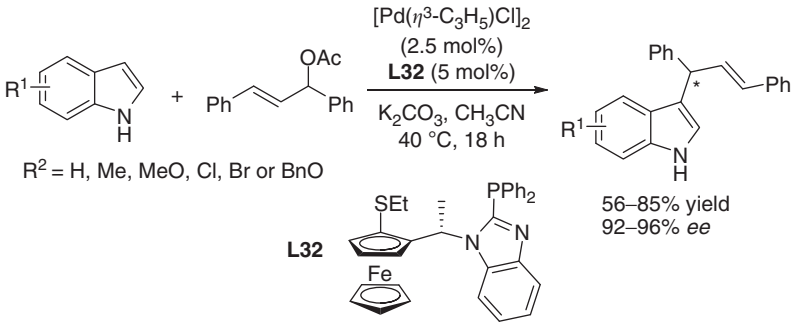


(70)

4.11.2.6 Aromatic Compounds

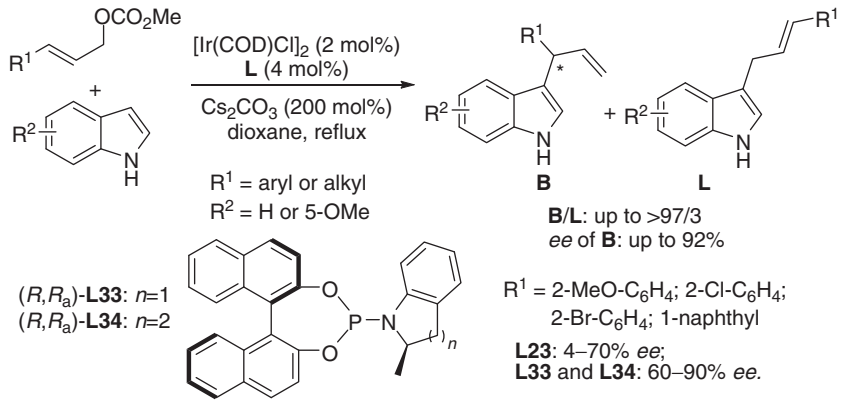
The use of electron-rich aromatics such as anisole and indole as nucleophiles for allylic substitution was firstly reported by Kočovský and coworkers in 1999 under Mo(II)-catalyzed conditions.[133] Mechanistic studies revealed that the Mo(II) catalyst acted as a Lewis acid rather than a transition metal controlling the reaction. Umani-Ronchi and coworkers uncovered that the palladium

catalyst was efficient for the alkylation of indole with allylic carbonates.[134] Following their work, Chan and coworkers reported an AAA of indoles with 1.3-diphenylallyl acetate with a chiral ferrocene ligand **L32** (equation 71).[135] High enantioselectivities were achieved irrespective of the steric or electronic nature of indoles.



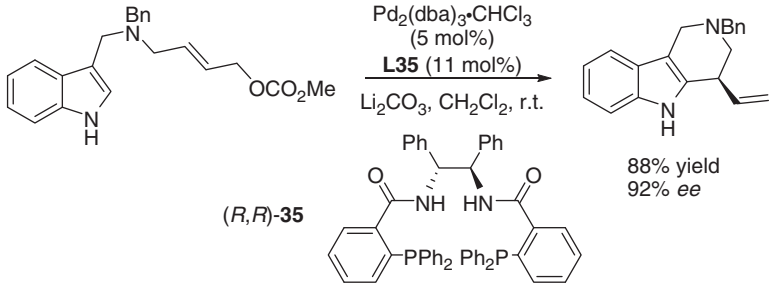
(71)

You and coworkers reported a regio- and enantioselective Friedel–Crafts-type allylic alkylation of indoles, affording the branched products with up to >97/3 branched-linear ratio and 92% *ee* (equation 72).[136] The reaction suffered from low enantioselectivity when the *ortho*-substituted cinnamyl carbonates were used as substrates. To address the issue, they devised new phosphoramidite ligands **33** and **34** from enantiopure BINOL and 2-methylindoline or 2-methyl-1,2,3,4-tetrahydroquinoline, which proved effective for *ortho*-substituted cinnamyl carbonates, providing a much higher enantioselectivity than ligand **23**.[137]

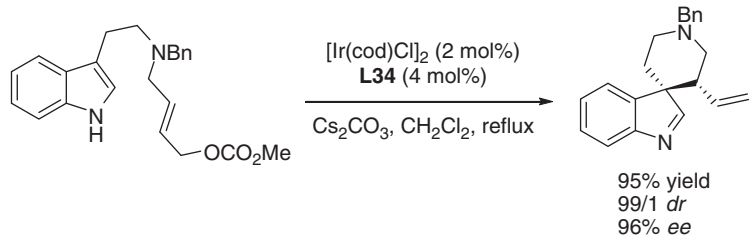


(72)

Intramolecular C-2 allylic alkylation of indoles was reported by Bandini and coworkers with a palladium catalyst (equation 73).[138] Trost's ligand led to tetrahydro-γ-carbolines with high levels of regio- and enantio-selectivities. By slightly modifying the substrate and using an iridium catalyst, You and coworkers realized an intramolecular C-3 allylic alkylation of indoles to afford a spiroindolenine (equation 74).[139] A 2-methyl-1,2,3,4-tetrahydroquinoline-derived phosphoramidite ligand (R,R_a)-**L34** gave excellent diastereo- and enantioselectivity. Bandini's substrate only gave the tetrahydro-γ-carboline product under Ir-catalyzed conditions. These results indicated that the formation of spiroindolenine was attributed to the favorable formation of a six-member ring by reacting at the C-3 position over the seven-member ring product by reacting at the C-2 position.

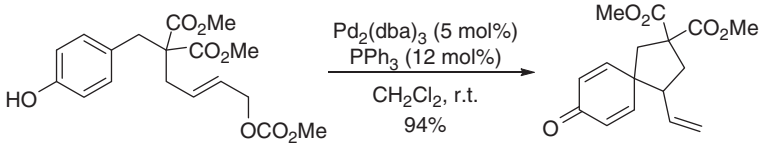


(73)

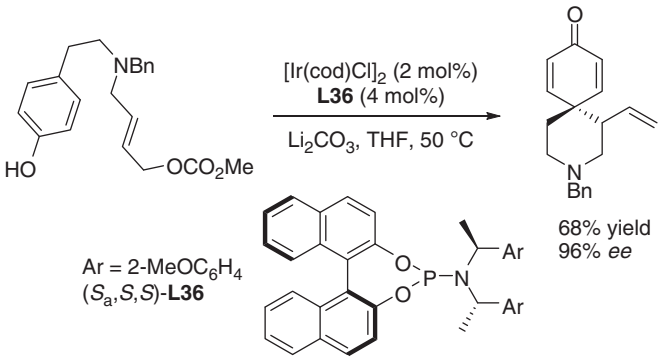


(74)

Phenols are the often used oxygen nucleophiles in transition metal-catalyzed allylic alkylation. Hamada and coworkers reported a Pd-catalyzed intramolecular allylic alkylation of *para*-substituted phenol reacting at the aromatic *ipso*-carbon, which afforded the corresponding Friedel–Crafts-type adducts, a spiro[4.5]cyclohexadienone (equation 75).[140] A catalytic asymmetric reaction for the synthesis of spirocyclic compounds bearing two contiguous chiral centers was also shown. The reaction was not appropriate for the formation of a six-membered ring product, only 5% yield of a spiro[5,5]cyclic adduct was obtained. These results indicated that the spiro-cyclization was highly dependent on the tether length between the phenol and the π-allylpalladium unit. One year later, You and coworkers demonstrated an iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of phenols (equation 76).[141] The reaction provided facile access to enantioenriched, substituted spirocyclohexadienone derivatives.

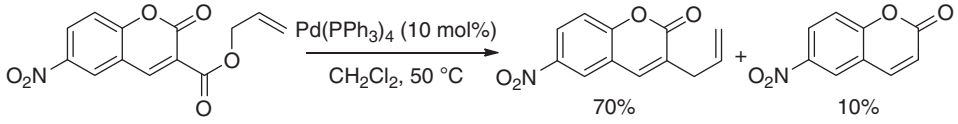


(75)



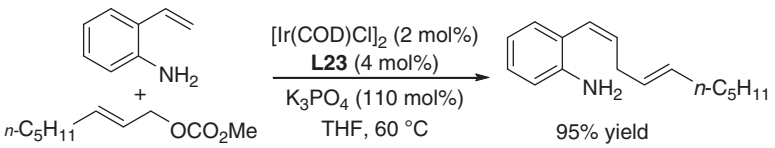
(76)

The decarboxylative alkylation of allylic esters of 3-carboxycoumarins using $Pd(PPh_3)_4$ constitutes a facial allylic alkylation of aromatic compound (equation 77).[142] The reaction also accompanied the apparent protonation of a vinyl anion equivalent to give 10% of 6-nitrocoumarin.

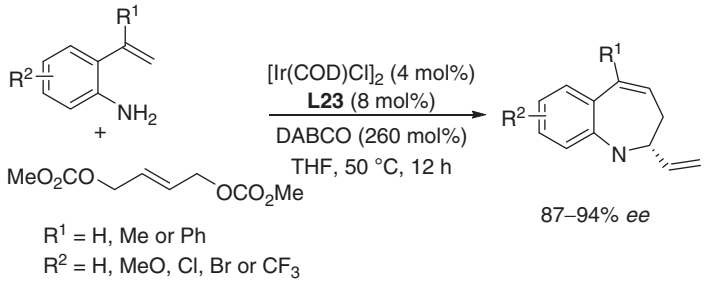


(77)

You and coworkers observed an unprecedented *cis*-Heck-type product, a skipped *Z*,*E*-diene, during the study of $[Ir(COD)Cl]_2$/**L23**-catalyzed allylic substitution reactions of *o*-amino styrene with allylic carbonates (equation 78).[143] Following the results, You and coworkers reported a tandem allylic vinylation and amination reaction of (*E*)-but-2-ene-1,4-diyl dimethyl dicarbonate with *ortho*-amino styrene derivatives, affording 2,3-dihydro-1*H*-benzo[*b*]azepines with high enantioselectivity (87–94% *ee*) (equation 79).[144]



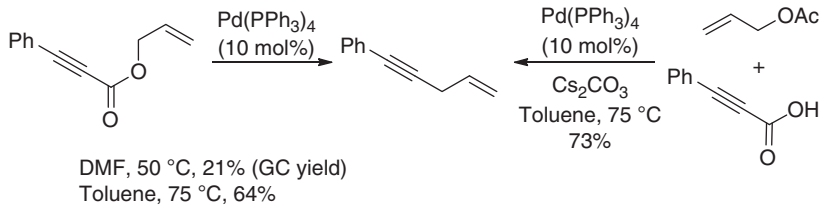
(78)



(79)

4.11.2.7 Acetylides

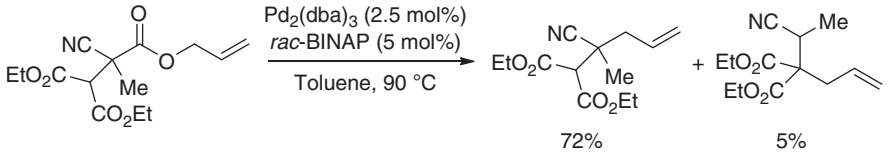
The use of acetylides as nucleophile for the transition metal-catalyzed allyl alkylation reaction involves an sp–sp^3 coupling reaction. Ikeda and coworkers reported a nickel-catalyzed cross-coupling reaction of allyl halides with alkynyltins using $P(OEt)_3$ as ligand.[145] Decarboxylative alkylation of a propiolic allyl ester under the Pd-catalyzed condition efficiently provided 1,4-enynes. This reaction avoided the use of toxic tin reagents. In 1980, Saegusa and coworkers reported a single example of such reaction but the yield was low (21% GC yield).[72] Rayabarapu and Tunge improved the yield of the reaction using toluene rather than DMF as solvent at a higher temperature (Scheme 17).[146] An intermolecular reaction between the propiolic acid and an allyl acetate could be achieved in similar yields with palladium catalyst, which obviated the precoupling of the two components. However, a stoichiometric amount of base was necessary to prevent the Pd-catalyzed decarboxylative protonation of propiolic acid.



Scheme 17

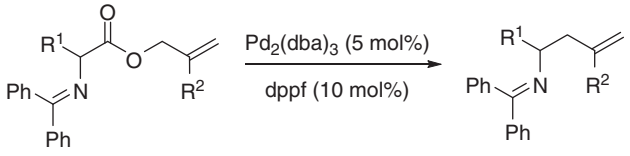
4.11.2.8 Other Carbon Nucleophiles

Decarboxylative coupling of an allyl cyanoaceticester is an efficient way to install an allyl group at the α-position of cyano functionality. The first example was reported by Saegusa and coworkers in 1980, in which the monoallylated product was obtained in 69% yield accompanied by 16% of the diallylated product.[72] Tsuji and coworkers disclosed two examples of a similar reaction and demonstrated that the reaction allowed the formation of a nitrile compound bearing α-quaternary carbon.[57] However, protonation of α-cyano anions was observed. Recio and Tunge found the use of *rac*-BINAP as the ligand could efficiently suppress the protonation product in decarboxylative allylations of α-cyanoacetic esters (equation 80).[147] For a substrate containing a more-acidic position, the decarboxylation alkylation regioselectively occurred at the α-position of cyanide. The formation of anions at the less acidic position was not accessible by standard acid–base chemistry.



(80)

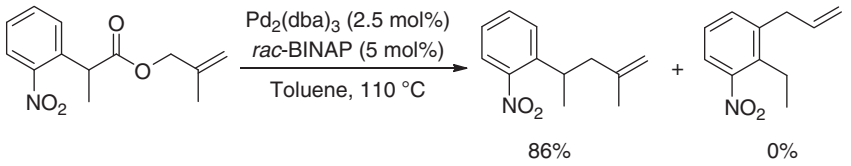
α-Imino anion equivalents is accessible by the decarboxylation of α-ketimine-protected amino allyl esters under the effect of palladium catalyst (equation 81).[148] Subsequent attack to electrophilic π-allylpalladium intermediates gives the homoallylic amines. The reaction of aryl amino acid derivatives could occur under mild conditions, whereas the alkyl-substituted analog required substantially harsh conditions. These results likely suggested the more difficult decarboxylation of α-alkyl imino acids.



(81)

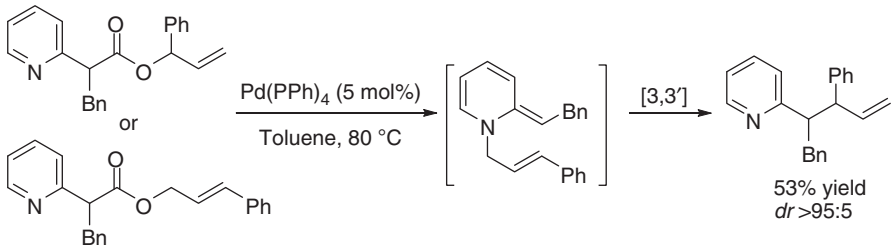
R^1 = Ph, R^2 = Me, THF, 40 °C, 81%
R^1 = ^{i}Bu, R^2 = Me or toluene, 110 °C, 26%

Nitro-substituted allylic ester undergoes a Pd-catalyzed decarboxylative allylation under Pd catalysis (equation 82).[149] The use of *para*-nitro analog results in a decrease of product ratio. The employment of a bidentate *rac*-BINAP ligand is critical to avoid the formation of a byproduct.



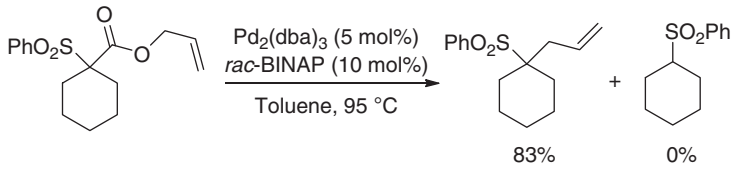
(82)

Decarboxylative alkylation of α-heteroaromatic acetic acids in the presence of palladium catalyst gives the allylated product of heteroaromatic alkanes as reported by Waetzig and Tunge (equation 83).[150] The reaction features the highly selective formation of the branched product. It was found that both branched and linear esters led to the same branched product. These results rule out the possibility of a Lewis acid-mediated Carroll-like rearrangement and indicate that a common Pd-π-allyl intermediate is formed in the reaction. The researchers propose that the reaction proceed by a unique allylation/aza-Cope rearrangement.



(83)

The allyl alkylation of α-sulfonyl anions is accessed indirectly by the decarboxylation alkylation of a fully substituted α-sulfonyl ester with palladium catalyst as reported by Weaver and Tunge (equation 84).[151] The use of bidentate ligands such as *rac*-BINAP could suppress the formation of undesired protonation products.

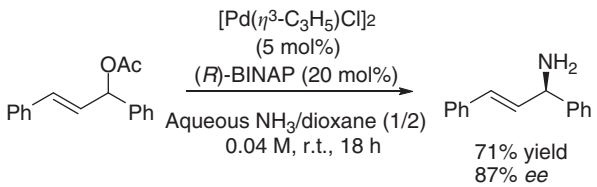


(84)

4.11.3 Nitrogen Nucleophiles

4.11.3.1 Ammonia and Amines

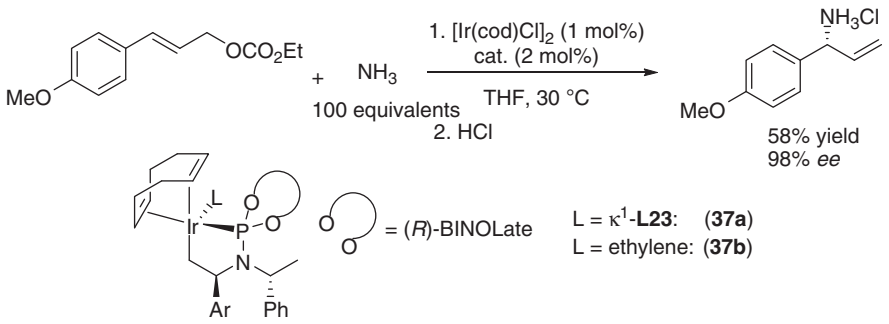
Although transition metal-catalyzed allylic amination is well known, the use of ammonia as a nucleophile is rare and challenging. The difficulty may arise from the deactivation of transition metal by ammonia poisoning. Nagano and Kobayashi developed the first example of palladium-catalyzed allylic amination with ammonia to produce primary amines (equation 85).[152] The use of aqueous ammonia as a nucleophile and the high dilution conditions are crucial. The ammonia gas did not react at all. With (*R*)-BINAP as chiral ligand, the asymmetric allylic amination proceeded smoothly to give primary allyl amine in 71% yield with 87% *ee*. The effective chiral induction suggested that these reaction conditions efficiently prevented ammonia poisoning.



(85)

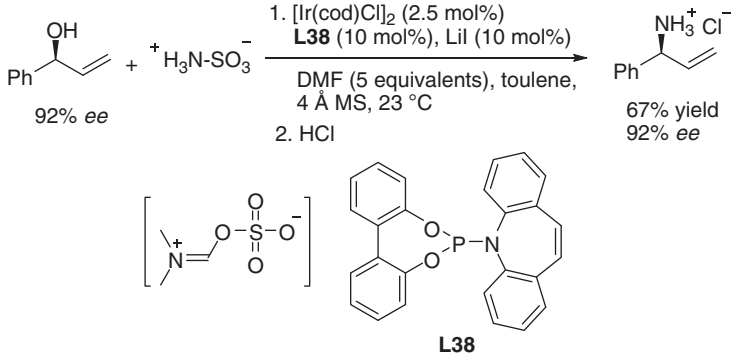
Hartwig and coworkers reported an iridium-catalyzed reaction of methyl cinnamyl carbonate with a dioxane solution of ammonia.[153] However, the diallylation product was obtained exclusively and no monoallylation product was observed. The results highlighted that the primary amine product of the reaction was much more reactive toward nucleophilic attack on an allyl ligand than ammonia. The same group addressed the problem using a high concentration of ammonia for selective formation of

primary allylic amines (equation 86).[154] Owing to the incompatibility of the reaction condition with activate catalyst **37a** because these complexes reacted with ammonia, a preprepared ethylene iridium complex **37b**, which was stable toward ammonia, proved efficient for the reaction between ammonia and ethyl cinnamyl carbonate. Quenching these reactions with acyl chlorides or anhydrides led to a one-pot synthesis of branched allylic amides.



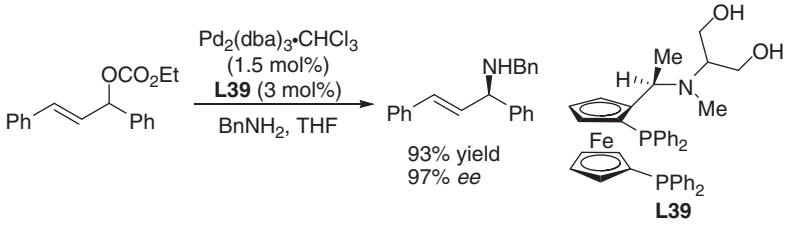
(86)

Roggen and Carreira documented a reaction of sulfamic acid, an ammonia equivalent, with allyl alcohols in the presence of iridium catalyst (equation 87).[155] The reaction provided a facial route for the stereoselective synthesis of primary amines. *N*,*N*-Dimethylformamide was proposed to react with sulfamic acid to form Vilsmeier-like-intermediate, which was reactive intermediate. Another key aspect of the reaction was the addition of iodide (such as LiI, NaI, KI, CsI, Bu_4NI) uniformly resulting in an increase in the optical purity of the product.



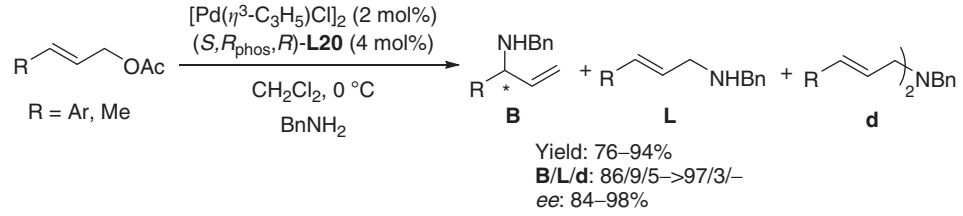
(87)

The asymmetric allylic amination between benzylamine and 1,3-disubstituted allylic substrate under the effect of palladium catalysis was reported by Hayashi, Ito, and coworkers in 1989 (equation 88).[156] The ferrocenyl phosphine **L39** with a pendant side chain bearing a hydroxy group proved to be an optimal ligand. The terminal hydroxy group on the ligand directs the incoming amine attacked on one of the π-allyl carbons. The key role of the hydroxy group was supported by an X-ray structure analysis of a π-allylpalladium complex and ^{31}P NMR studies.

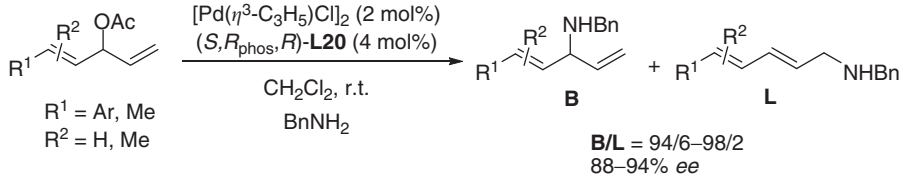


(88)

High regio- and enantioselectivities in Pd-catalyzed allylic amination of monosubstituted allyl acetates were also realized for a wide range of substrates using ferrocene L20 (*ee* ranging from 84% to 98%, the ratio of branch-linear up to 97/3) (equation 89).[37] The experiments demonstrated that the presence of the free hydroxyl group in the ligands was crucial for the stereoselectivity and reactivity of the reaction. When the ligand with OMe as protection of hydroxyl group was used, the reaction became sluggish and the regio- and enantioselectivities decreased dramatically. The 1,1′-*P*,*N*-ferrocene ligand SiocPhox L20 also showed excellent control of regio- and enantioselectivity in the amination reaction of pentadienyl branched allyl acetate with benzylamine (equation 90).[40]

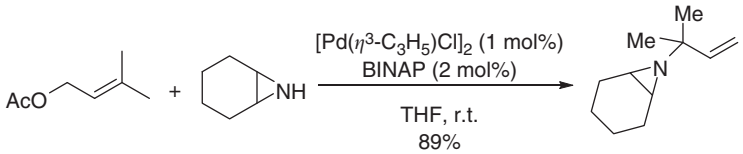


(89)

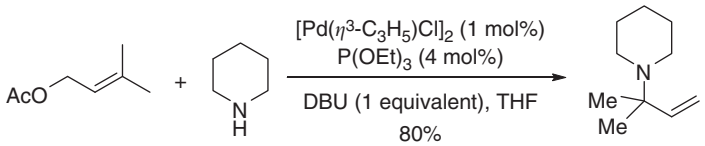


(90)

Yudin reported that unprotected aziridines underwent palladium-catalyzed allylic amination reactions with aliphatic allyl acetates to give branched products regioselectively (equation 91).[14a,b] In contrast, common secondary amines such as piperidine and benzylamine only gave the linear isomer under identical conditions. Mechanistic studies showed that branched (kinetically favored) products derived from common secondary amines rearranged into the linear (thermodynamically favored) products under palladium catalysis. Such isomerization process did not occur for the branched allylic products obtained from unsubstituted aziridines. The branched allyl aziridines against palladium-catalyzed isomerization is due to a combination of factors that stem from a higher degree of *s*-character of the aziridine nitrogen compared with other amines. The protic acid formed during the reaction was the prerequisite for product isomerization. Yudin and coworkers uncovered that the presence of DBU could scavenge the proton and had no detrimental effect on catalytic turnover. The modification of reaction condition suppressed the formation of a linear product and allowed the synthesis of branched allyl amine from common primary and secondary amines (equation 92).[14c]

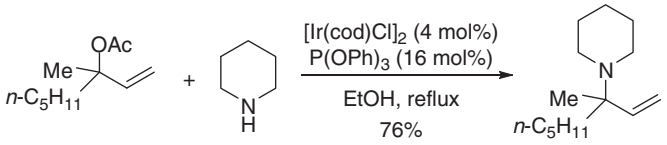


(91)

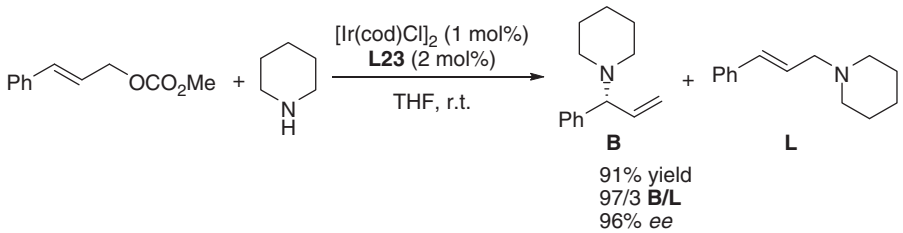


(92)

Takeuchi and coworkers reported that both secondary and primary amines reacted regioselectively with allylic carbonates in the presence of a catalytic amount of $[Ir(COD)Cl]_2$ and $P(OPh)_3$ to give a branch amine with up to 99% selectivity (equation 93).[157] The reactivity of the reaction was strongly affected by the solvent: the use of a polar solvent such as EtOH was essential for obtaining the products in high yields. The reaction of 1,1-disubstituted-2-propenyl acetate with amines exclusively gave an α,α-disubstituted allylic amine. Following these results, Ohmura and Hartwig developed an asymmetric version of the reaction with excellent enantioselectivity (equation 94).[158]



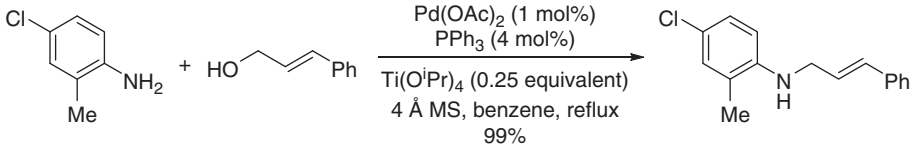
(93)



(94)

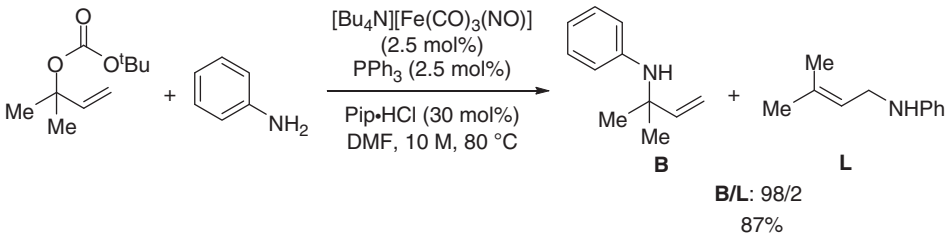
4.11.3.2 Aromatic Amines

In contrast to alkyl amines, there are much less examples of using aromatic amines as nucleophiles in transition metal-catalyzed allylic substitution, presumably due to the lower nucleophilicity of an arylamine relative to an alkyl amine. The early example of such reaction usually utilized allylic alcohol derivative as substrates. Yang and Hung reported the first example of palladium-catalyzed allylation of anilines by the direct use of allylic alcohols as electrophile in the presence of $Ti(OPr^i)_4$ (equation 95).[159] Owing to the fact that OH group is a poor leaving group, the allylic alcohol was *in-situ* activated with the aid of Lewis acid. Ozawa developed a (π-allyl)palladium complex bearing diphosphinidene cyclobutene ligand, which could effectively catalyze the direct reaction of allylic alcohols with aniline in the absence of external activating agents.[160]



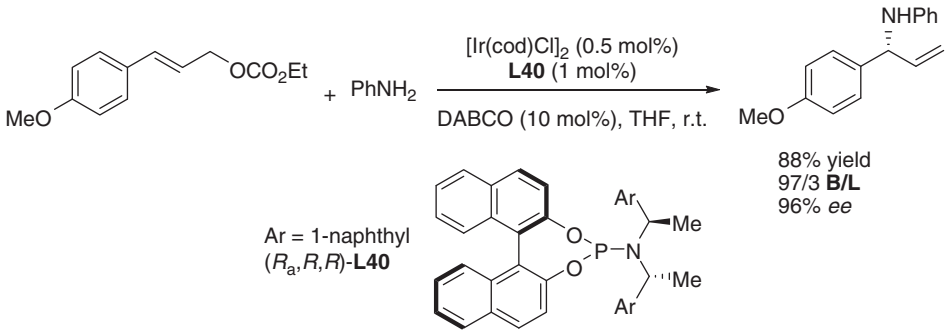
(95)

Plietker reported a $[Bu_4N][Fe(CO)_3(NO)]$-catalyzed regioselective allylic amination of aniline (equation 96).[161] The reaction features a high degree of regioselectivity in favor of the *ipso*-substitution product. The addition of piperidinium chloride (Pip·HCl) as a buffer efficiently prevented the iron catalyst from decomposition. A high concentration of the substrate was also crucial to realize a full conversion of the reactants. The reaction allowed the facial selective preparation of α,α-disubstituted allylic amines.



(96)

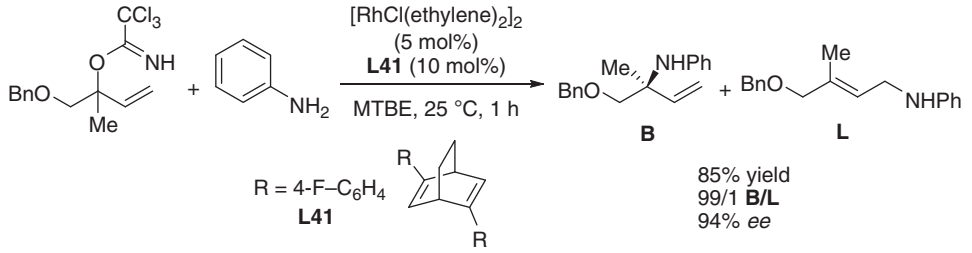
Hartwig and coworkers initially observed that the reactions between aromatic amines and allylic carbonates did not occur in the presence of an iridium complex with a phosphoramidite ligand.[162] The mechanistic studies demonstrated that the cyclometalated complex, generated *in situ* by treatment of $[\{Ir(cod)Cl\}_2]$ (cod = cycloocta-1,5-diene) and the ligand **L23** with an alkylamine base, is likely to be an active catalyst in the allylic amination of alkyl amines. The researcher used the pregenerated active cyclometalated complex or a catalyst generated *in situ* by the action of an external additive to develop a general reaction of allylic carbonates with aromatic amines, which gave branched chiral allyl aryl amines in excellent yields with high regio- and enantioselectivities (equation 97).[163] The same group revealed that the reaction could be extended to the use of allyl alcohol as electrophile. However, this reaction needs the addition of a stoichiometric amount of $Nb(OEt)_5$ or a catalytic amount of BPh_3.[164] The palladium catalyst was also employed for asymmetric catalytic amination with arylamines, but the substrate scope is much limited.[165]



(97)

Arnold and Nguyen developed a rhodium-catalyzed regio- and enantioselective amination of racemic tertiary allylic trichloroacetimidates with a variety of aniline nucleophiles (equation 98).[166] The reaction proceeded through a dynamic kinetic asymmetric transformation (DYKAT) of racemic tertiary allylic electrophiles with anilines utilizing a chiral diene-ligated rhodium

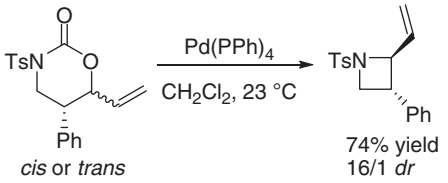
catalyst. The method allows the formation of α,α-disubstituted allylic *N*-arylamines in moderate to good yields with good to excellent levels of regio- and enantioselectivities.



(98)

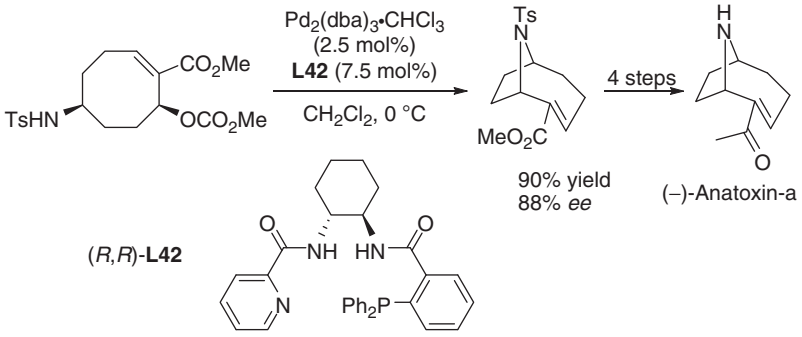
4.11.3.3 Amides

Alkyl sulfonamides are good nucleophiles for transition metal-catalyzed allylic amination reaction. Wang and Tunge revealed that 6-vinyl oxazinanones underwent a Pd-catalyzed diastereoselective and decarboxylative ring contraction to give vinyl azetidines via intramolecular attack of sulfonamide anions on the palladium π-allyl ligands (equation 99).[167] The *trans*-vinyl azetidine was formed rapidly from either the *trans*- or *cis*- carbamate in a 16:1 *dr*. This result clearly demonstrated that π-allylpalladium isomerization, via π–σ–π epimerization, proceeded faster than the C–N bond formation.



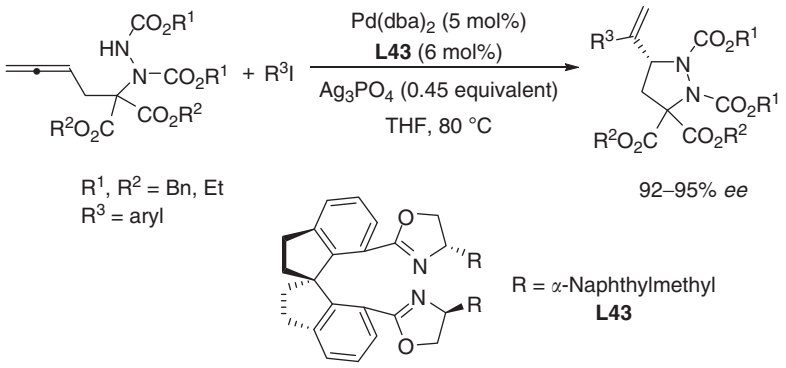
(99)

Trost and Oslob developed an interesting intramolecular Pd-catalyzed allylic amination reaction of sulfonamide in the context of medium-sized ring substrates (Scheme 18).[168] The standard Trost ligand showed poor reactivity. A mixed *P,N*-ligand by reducing the steric demand and increasing the donor property allowed the reaction to proceed at 0 °C. The desired product was afforded in high yield and enantioselectivity. This protocol allowed for the asymmetric synthesis of (−)-anatoxin-a.



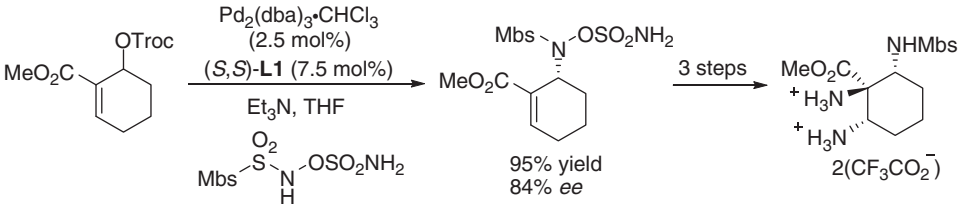
Scheme 18

Ma and coworkers reported an enantioselective cyclic allylation based on the carbopalladation of 3,4-allenyl hydrazines using a catalyst from the Pd(0)/bisoxazoline ligand **L43** with a spiro skeleton and a α-naphthylmethyl substituent (equation 100).[169] The optically active pyrazolidine derivatives were obtained with *ee* values ranging from 92% to 95%. The reaction may proceed via oxidative addition, intermolecular carbometallation of the allene moiety forming a π-allylpalladium intermediate, and intramolecular enantioselective allylation.



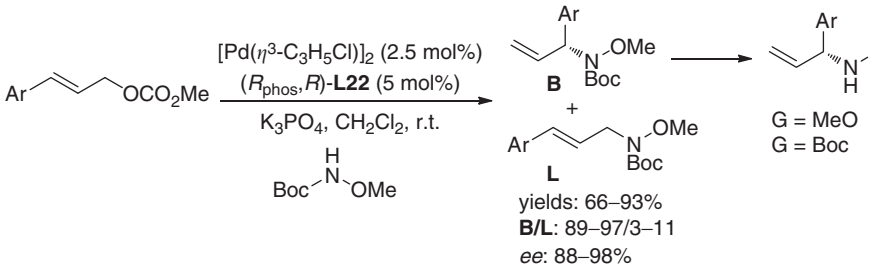
(100)

Hayashi and coworkers reported the intermolecular asymmetric amination between 1,3-diphenyl allyl substrate and *p*-toluenesulfonamide to give the corresponding allylamines with 88% *ee* and in 67% yields.[156] Stragies and Blechert reported that an alkyl-substituted secondary nosyl sulfonamide was used in the palladium-catalyzed desymmetrization of a five-membered cyclic meso-carbonate.[170] The resulting product was key intermediate in the enantioselective synthesis of tetraponerines. Hydroxylamine-*O*-sulfamates participated in chemoselective Pd-catalyzed AAA-reactions, where the hydroxylamine functionality preferentially acted as the nucleophile over the sulfamate moiety (Scheme 19).[171] The product was further elaborated to unnatural triaminoester in an enantioenriched form.



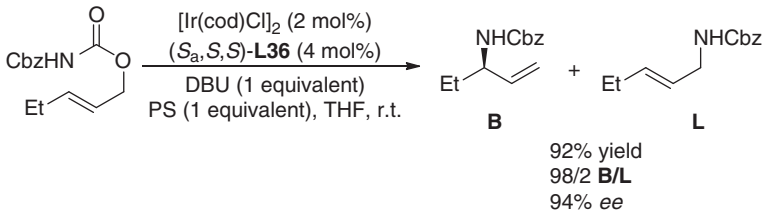
Scheme 19

Hydroxylamines can be used as nitrogen nucleophiles in allylic substitutions with regio- and enantioselective control using an iridium catalyst. The branched products were formed with good enantioselectivities,[172] whereas in palladium-catalyzed amination the allylic substitution with hydroxylamines generally give a linear product.[173] Hou and coworkers developed a regio- and enantioselective Pd-catalyzed allylic amination of monosubstituted allylic substrates with BocNHOMe (Scheme 20).[174] The corresponding branched allyl amines were afforded in high regio- and enantioselectivities. Either OMe or Boc group in products can be removed easily to provide the primary amine derivatives with the optical purity remaining unchanged.



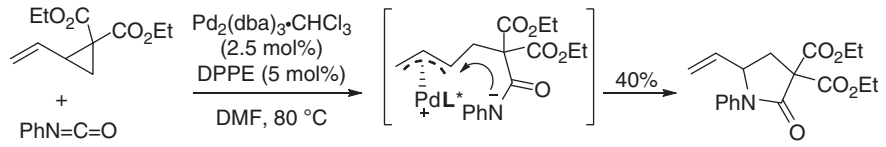
Scheme 20

In 2007, Singh and Han reported an asymmetric Ir(I)-catalyzed decarboxylative amidation of Cbz-protected allylic carbamates.[175] The decarboxylative amination provided access to highly enantioenriched allylic carbamates that can be readily deprotected to form allylic amines (equation 101). The addition of an equivalent of DBU as well as proton sponge (PS) efficiently promoted the reaction. Mechanistic studies showed that the reaction proceeded via π-allyl iridium intermediates rather than through a [3,3]-rearrangement, and C–N bond formation occurs before decarboxylation. Hartwig and coworkers developed a direct allylic substitution with commercially available carbamate nucleophiles.[176] The reaction avoided the presynthesis of imido dicarbonates which was used in the decarboxylative amination, but the regioselectivity was not as high as that of the decarboxylative processes.

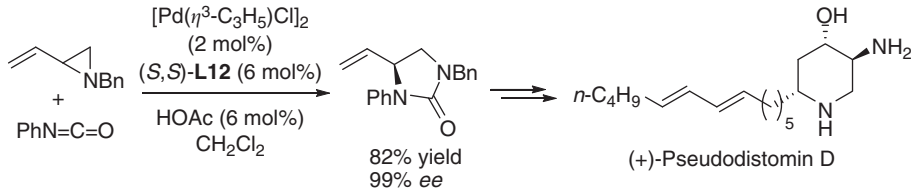


(101)

In 1987, Tsuji and coworkers reported the reaction of activated vinyl cyclopropane and phenyl isocyanate with Pd(0) complexes as a catalyst formed a π-allylpalladium complex bearing an amide nucleophile.[177] The intermediate underwent an intramolecular allylic substitution reaction to give a five-membered cycloaddition product (equation 102). Baeg and Alper found that bis(benzonitrile)palladium dichloride was an effective catalyst for the cycloaddition reaction of aziridines with carbodiimides to form imidazolidinimines.[178] The use of enantiomerically pure 1,2-disubstituted aziridines led to the corresponding chiral five-membered ring heterocycles with retention of configuration. Alper group also reported that 2-vinyloxiranes underwent palladium (0)-catalyzed asymmetric cycloaddition with isocyanates and carbodiimides to form oxazolidinones and oxazolidinone imines, respectively.[179] This reaction was also applicable to vinyl aziridine and phenylisocyanate.[180] The presence of Trost's ligand enabled the corresponding imidazolidin-2-one product obtained in excellent enantioselectivity. The protocol was applied to a concise total synthesis of (+)-pseudodistomin D (**Scheme 21**).

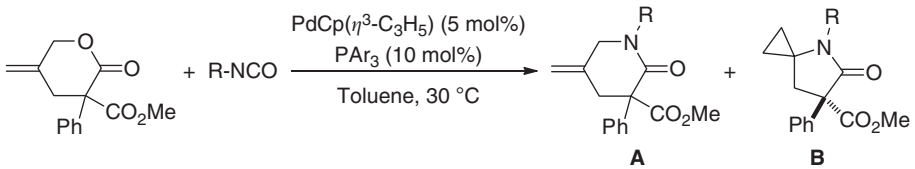


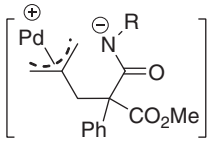
(102)



Scheme 21

Palladium-catalyzed decarboxylative reaction of γ-methylidene-δ-valerolactones followed by the reaction with isocyanate formed an intermediate containing an amide anion nucleophile (**Scheme 22**).[181] The intramolecular substitution reaction could occur at the terminal or center position of π-allylpalladium complex, providing allylic substituted products or cyclopropanes. The regioselectivity of the lactamization is affected by the electronic effects imparted by the ligand on the metal center. Nucleophilic attack at the terminal carbon of the π-allylpalladium complex was favored using an electron-rich aryl-substituted phosphine. In contrast, the use of electron-deficient aryl-substituted phosphines favored nucleophilic attack at the central carbon of the π-allylpalladium complex. These results suggest that minor alteration of ligand electronics greatly influences the electrophilicity of the central and terminal carbons of the π-allyl metal complex, which in turn has a significant influence on the regiochemistry of nucleophilic substitution.

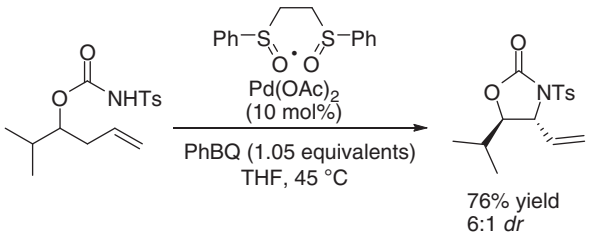




Entry	Ar	R	yield (%)	**A/B**
1	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	87	>99/1
2	4-CF$_3$C$_6$H$_4$	4-MeOC$_6$H$_4$	73	5/95

Scheme 22

Fraunhoffer and White developed a Pd/sulfoxide catalyzed diastereoselective intramolecular allylic amination reaction of chiral homoallylic *N*-tosyl carbamates (equation 103).[182a] The use of the weak nitrogen nucleophile efficiently avoided the formation of the aza-Wacker reaction products. The corresponding chiral oxazolidinone product was obtained in high yield and diastereoselectivity controlled by the stereocenter bearing the *N*-tosyl carbamates. The products could be elaborated to synthetically useful 1,2-amino alcohols. Liu et al. developed a palladium-catalyzed intramolecular aerobic oxidative allylic C–H amination of olefins. The presence of Brønsted base favors the formation of seven-membered cyclic amides. Mechanistic studies revealed a rate-determining allylic C–H activation/irreversible reductive elimination pathway.[182b]

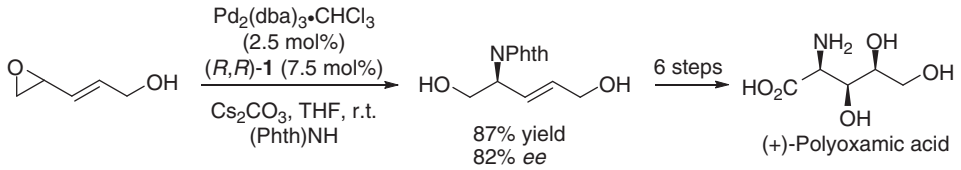


(103)

The catalytic intermolecular allylic C–H amination reaction was reported by two groups independently in 2008.[182c,d] Reed and White used a heterobimetallic Pd(II)-Cr(III) catalytic system.[182c] Mechanistic studies revealed each metal effects different product-forming steps in the catalytic cycle. The Pd catalyst mediates allylic C–H cleavage to form a π-allylPd complex that was isolated and characterized, whereas Cr catalyst and BQ promote C–N bond formation via attack of *N*-nucleophile to π-allyl-Pd complex. Liu and coworkers used $Pd(OAc)_2$ as the catatlyst, dioxygen as oxidant, and maleic anhydride as the additive.[182d] A mechanism involving π-allylpalladium intermediates also was suggested. The maleic anhydride is proposed to play a role at facilitating nucleophilic attack on the π-allylpalladium species. Later, Liu group used a strong soluble oxidant $PhI(OPiv)_2$ to replace dioxygen and performed systematic analysis of the mechanism of the allylic C–H oxidative amination.[182e] It indicated that the turnover-limiting step is olefin coordination to palladium catalyst in the absence of any quinone. However, naphthoquinone (NQ) can promote olefin coordination to the palladium catalyst. A nitrogen-coordinated olefin-Pd(NQ) complex was the key intermediate when allylic C–H bond activation occurs to generate a π-allyl-Pd intermediate.

4.11.3.4 Imides

The delocalization of electron density on nitrogen into the attached carbonyl or sulfonyl groups of the imide enables it become a 'soft' nucleophile. Thus, imides have been extensively utilized as nucleophiles for AAA reactions. Among all imide nucleophiles, phthalimide is the most commonly used nitrogen nucleophile because of its excellent reactivity, the phthaloyl group on the resulting allylic amine product serves as a convenient protecting group for the amino moiety. Trost and coworkers reported that phthalimide serve as an excellent nucleophile for vinyl epoxide (**Scheme 23**).[31a] The method led to an enantioselective synthesis of (+)-polyoxamic acid.

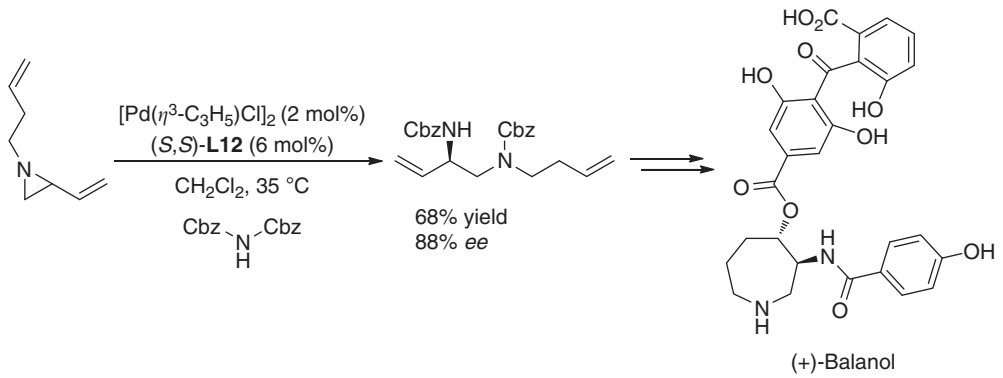


Scheme 23

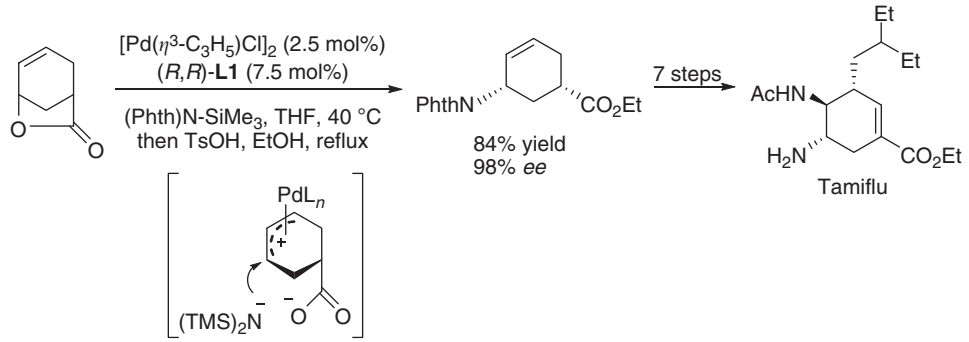
Vinyl aziridines have proven to be particularly useful substrates, providing products attacked at the more substituted terminus by the imido carboxylates under the effect of palladium catalysis (**Scheme 24**).[183] The method allows facial preparation of chiral vicinal diamines and amino alcohols through a dynamic kinetic asymmetric allylic amination and acyl migration of vinyl aziridines and epoxide with imidocarboxylates. The protocol also resulted in an enantioselective synthesis of (+)-balanol.

The reaction using a lactone as the allylating reagent and phthalimide as the prenucleophile led to no reaction with or without base. These results may be due to the repulsion induced from the negative charge on the nitrogen atom and that on the carboxylate group, which thus make the nucleophilic substitution unlikely. To eliminate such repulsion, the researchers used *N*-trimethylsilyl phthalimide as the substrate. The silyl group was transferred to carboxylate anion, thus generating the imide anion simultaneously. Under these conditions, the reaction proceeds smoothly to give the alkylated phthalimide in 98% *ee*, a key intermediate for a very short synthesis of the antiviral agent tamiflu (**Scheme 25**).[184]

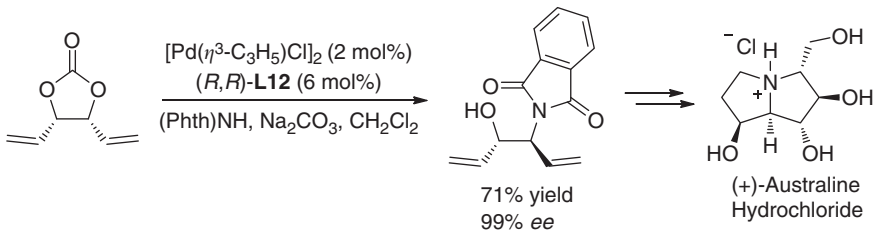
A *meso*-cyclic carbonate derived from the meso-diastereomer of 3,4-dihydroxy hexa-1,5-diene gave the monoalkylated product using phthalimide as the nucleophile in perfect regio- and enantioselectivity (**Scheme 26**).[185] The resultant product served as a key intermediate for the synthesis of the pyrrolizidine alkaloid australine.



Scheme 24



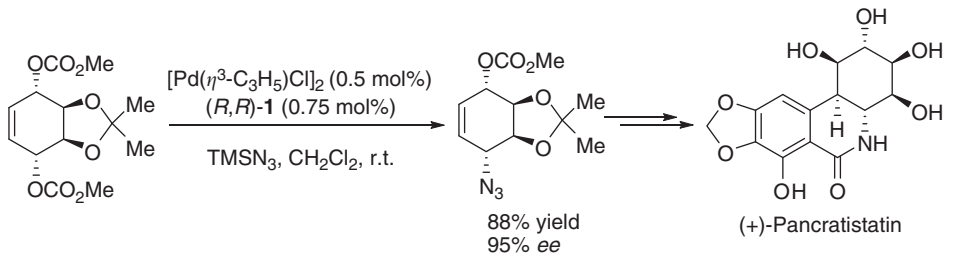
Scheme 25



Scheme 26

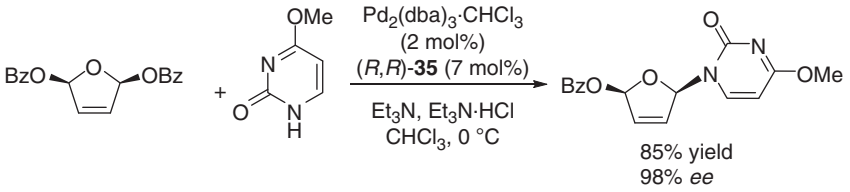
4.11.3.5 Other Nitrogen Nucleophiles

Azide proved to be a most interesting nitrogen nucleophile. An advantage of the azide is its excellent nucleophilicity and ease of reduction. Trost and Pulley reported that desymmetrization of a heavily substituted substrate with azide proceeded efficiently to produce the desired alkyl azide, which was a key intermediate toward the synthesis of the antitumor agent pancratistatin (Scheme 27).[186] The acetonide group should not hinder the approach of the palladium catalyst to the double bond as the palladium must attack the same face of the double bond proximal to the acetonide.



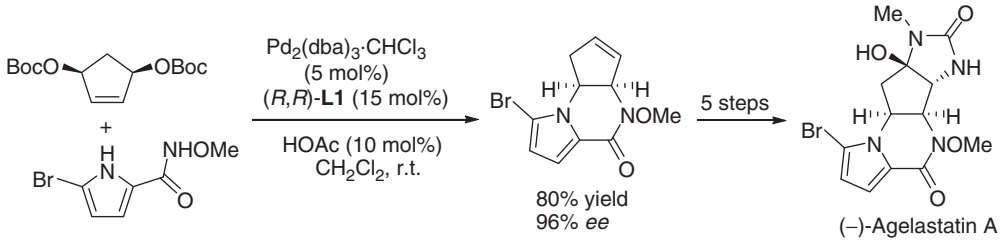
Scheme 27

Heterocycles stabilized by delocalization constitute another category of good nucleophiles for AAA reactions. Trost and Shi reported the first example of performing a Pd-catalyzed desymmetrization of meso-dihydrofuran with 4-methoxypyrimidone as the nucleophile (equation 104).[187]



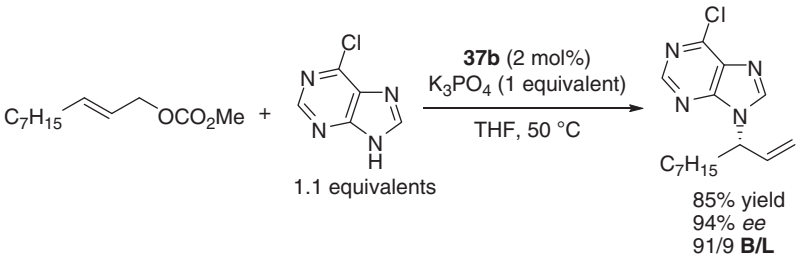
(104)

A bis-*N*-nucleophile containing both pyrroles and *N*-methoxyamide proceeded through a one-pot cascade palladium-catalyzed allylic substitution reaction (Scheme 28).[188] The initially formed monoalkylation product spontaneously cyclized under the reaction conditions to form the tricyclepyrrolopiperazinone, an intermediate on the way to agelastatin A.



Scheme 28

The reaction of purines with methyl allylic occurred with regioselective and enantioselective control in the presence of single component, ethylene-bound, metallacyclic iridium catalysts. *N*-allylated purines were obtained in high yields with high N9/N7 selectivity (93:7), high branched-to-linear selectivity (91:9), and high enantioselectivity (94% *ee*) (equation 105).[189]

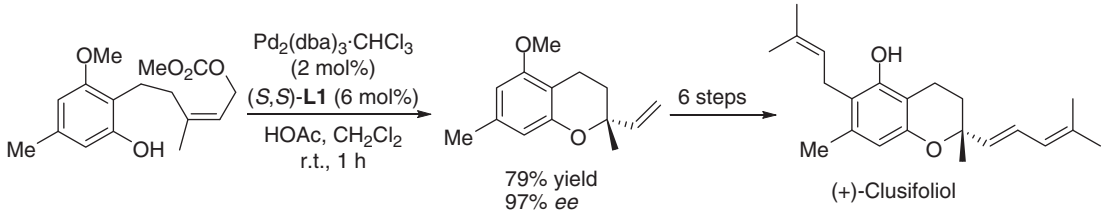


(105)

4.11.4 Oxygen Nucleophiles

4.11.4.1 Phenol

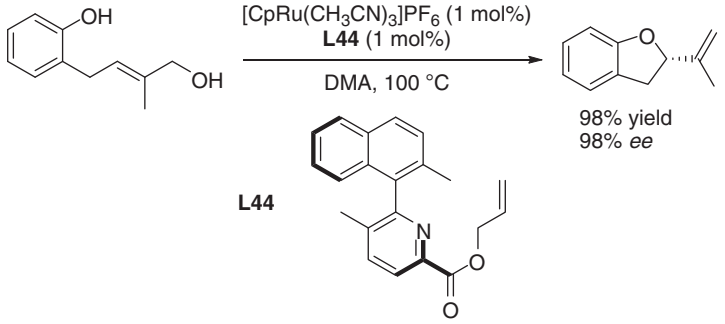
Intramolecular allylic alkylation of phenols is an efficient route to chromans. The early examples from the groups of Achiwa and Sinou afforded limited substrate scope with modest *ee*.[190] Trost and coworker revealed that the geometry of alkenes and additives have great impact on the enantioselectivity (Scheme 29).[191] *Z*-trisubstituted olefins gave significantly higher *ee* than their *E* counterparts. However, *E*-disubstituted olefins gave substantially higher *ee*'s than their Z counterparts. A dramatic increase of the *ee* was also observed with one equivalent of acetic acid as additive. The chiral chromanes prepared in 97% *ee* via oxygen attack at the



Scheme 29

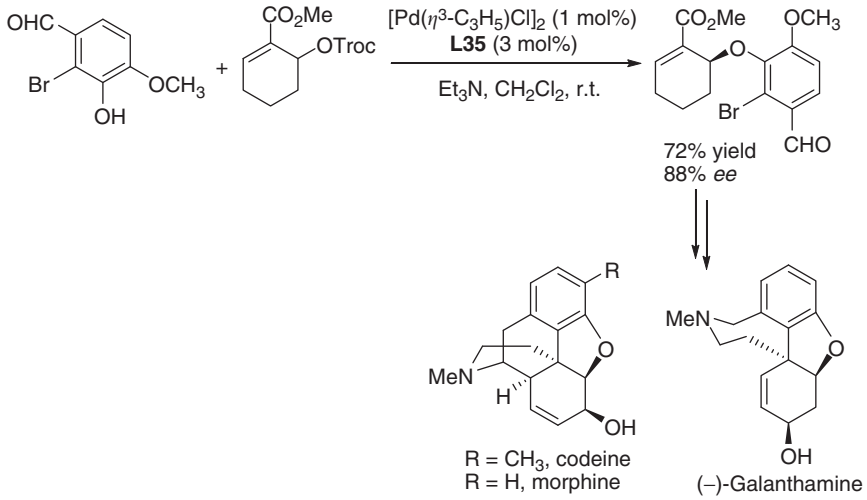
more substituted tertiary terminus were applied to a total synthesis of (+)-clusifoliol, a constituent of a folk medicine used to treat malignant tumors.

Kitamura and coworkers have reported that ω-hydroxy allyl alcohols underwent a dehydrative intramolecular cyclization with excellent reactivity and stereoselectivity (equation 106).[192] Both aliphatic alcohols and phenols can be used as nucleophiles at the ω-hydroxy end of the substrate. An unprecedented reaction of CpRu(IV)–π-allyl carboxylato complex, synthesized *in situ* from the chiral allylic pyridine-2-carboxylic ester **L44** and $[CpRu(CH_3CN)_3]PF_6$ (Cp = cyclopentadienyl), provided cyclic ethers in a highly stereoselective manner (>98% *ee*).



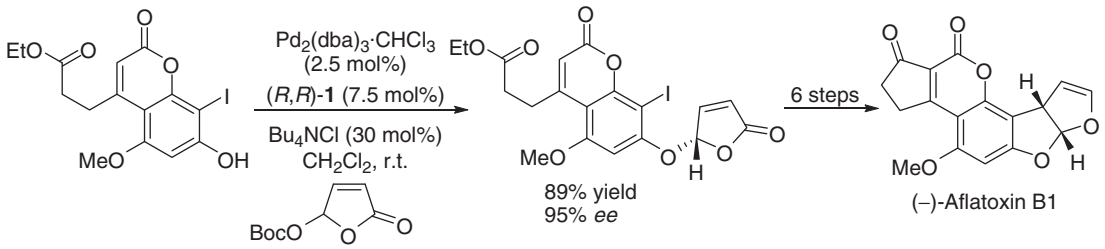
(106)

Asymmetric intermolecular allylic alkylation with phenol nucleophiles is firstly developed by Trost and Toste (**Scheme 30**).[193] A heavily substituted phenol reacted with ester-substituted allyl substrate in the presence of palladium catalyst to furnish the aryl ether in 72% yield and 88% enantiomeric excess. It is noteworthy that the reaction could be scaled up to 24 mmol scale. The resultant product proved to be a common intermediate toward galanthamine, an inhibitor of AChE for the treatment of Alzheimer's, and morphine, is one of the most important analgesics.



Scheme 30

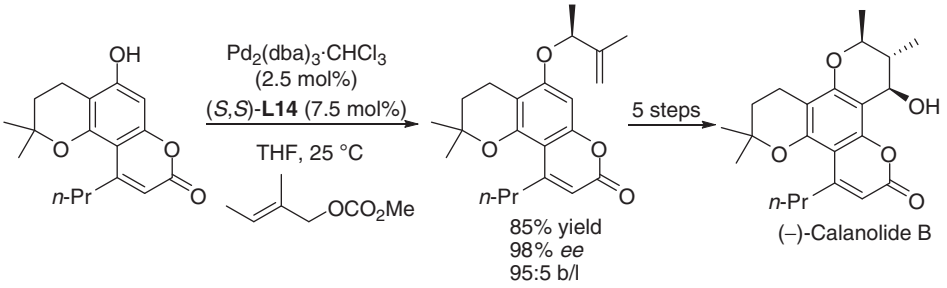
The reaction of phenol nucleophile with γ-*tert*-butoxycarbonyloxy-2-butenolide in the presence of a Pd(0) complex with chiral ligands was greatly influenced by the reaction conditions (**Scheme 31**).[194] A DYKAT is favored by the addition of soluble chloride ion source such as *tetra*-butylammonium chloride that facilitated the conversion of the π- to σ-allyl complexes and thus the rate of



Scheme 31

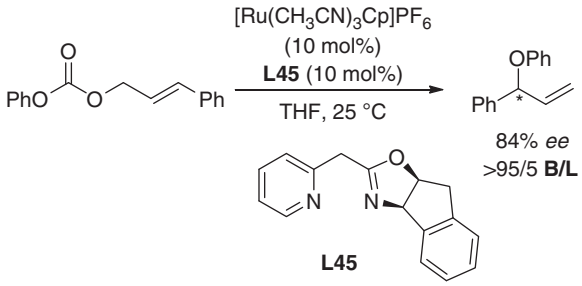
racemization of the intermediate allyl complex. This enantiodiscriminating mechanism is illustrated in the asymmetric inducing event in the synthesis of (−)-aflatoxin B1.

The phenol can attack the more substituted terminus of monosubstituted π-allylpalladium complex (Scheme 32).[195] In the reaction, the chiral pocket of the ligand rather than the substrate dictates both the regio- and enantioselectivity of the *O*-alkylation. Coordination of a palladium complex to a less substituted double bond is favored both electronically and sterically, which then directs the nucleophile to the more substituted allylic terminus. This *O*-alkylation has been used to perform a synthesis of calanolide B.



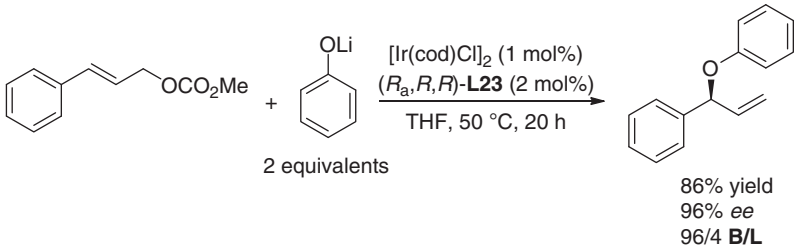
Scheme 32

Decarboxylative alkylation is an alternative access to aryl allyl ethers. Rama and coworkers initially uncovered that Ni, Pd, and Rh catalysts are able to catalyze the asymmetric decarboxylative alkylation of crotyl phenyl carbonates.[196] Interestingly, the branched product was formed as the major product using these metals. Lacour and coworkers realized an asymmetric decarboxylative alkylation of aryl allyl carbonates with a ruthenium catalyst (equation 107).[197] High *ee*'s and conversions were observed. The chiral branched product could be rearranged into a thermodynamic linear product by the ruthenium catalyst due to reversibility of the C–O bond formation. Trivedi and Tunge demonstrated that an anionic iron catalyst could catalyze the decarboxylative alkylation of allylaryl carbonates to form allylic ethers in high yields.[198] The reaction is regioselective rather than regiospecific, giving the same regioisomeric product regardless of whether the linear or branched carbonate reactant was used. These results may suggest that the allylation proceeds through π-allyl iron intermediates.



(107)

Hartwig and coworkers demonstrated that lithium and sodium phenolates regioselectively attack the more substituted terminus of the π-allyl iridium complex (equation 108).[199] The branched allylic ethers were obtained in high yield with high branched-to-linear ratios, and enantiomeric excesses of up to 97%. The use of alkali metal phenoxides as nucleophile was crucial for the reaction. The reaction using phenols in combination with organic amine bases resulted in a lower yield and enantioselectivity.



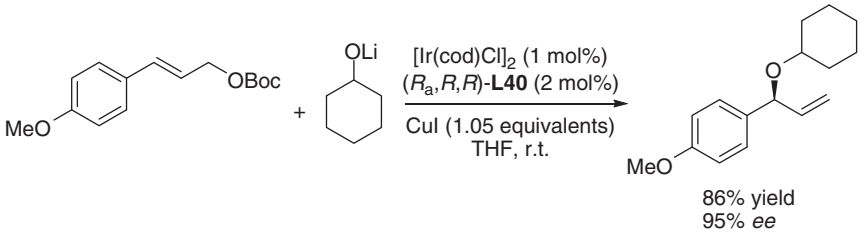
(108)

4.11.4.2 Alcohol Nucleophiles

Aliphatic alcohols and alkoxides are poor nucleophiles in AAA reactions. When an alkali alkoxide is used as the nucleophile, elimination and deactivation of the metal catalyst occurred. Activation of the reaction system toward alcohol attack or softening of

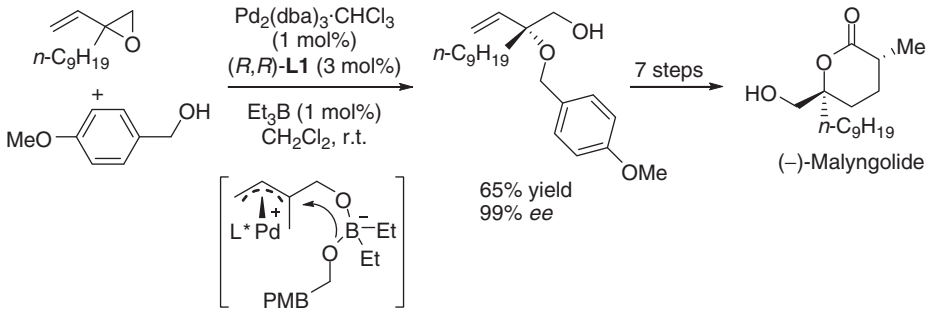
the alkoxide nucleophile could potentially overcome these problems. Decarboxylative alkylation of allyl alkyl carbonates is an alternative for preparing allylic alkyl ethers. An early and single example of such reaction was reported by Guibe and M'Leux in 1981.[200]

Shu and Hartwig revealed that the copper salts could soften the hard alkoxide nucleophile. The allylic etherification of *in-situ* formed softer copper alkoxide occurred with high yield and enantioselectivity in the presence of iridium–phosphoramidite catalyst (equation 109).[201] The reaction tolerated electron-rich, electron-neutral, and electron-poor cinnamyl carbonates as well as alkyl-substituted allylic carbonates and afforded branched products in high yields and enantioselectivities. Zinc alkoxides are also effective nucleophiles in allylic etherification reactions.[202] The cross-coupling reaction between various aliphatic alcohols and allylic acetates proceeded at ambient temperature to furnish allylic ethers with high stereoselectivity.



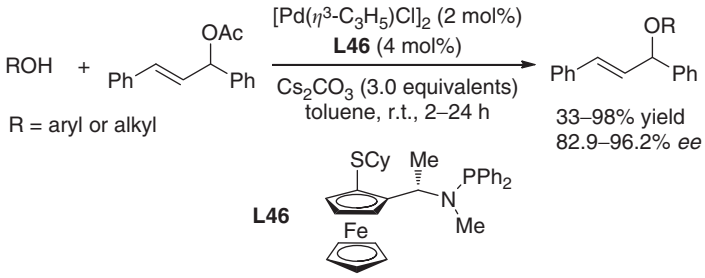
(109)

Alcohols have also been used directly in intermolecular allylic etherification. Trost and coworkers uncovered that a catalytic amount of trialkylborane was competent for promoting the Pd(0)-catalyzed nucleophilic addition of alcohol to vinyl epoxide (Scheme 33).[203] The reaction proceeded chemo-, regio-, and enantioselectively via a borate intermediate generated *in situ* to furnish the branched products. For example, the reaction of 3-nonyl-3,4-epoxybut-1-ene with *p*-methoxybenzyl alcohol gave the monoprotected vinyl glycidol in 99% *ee*. This chiral building block was elaborated to (−)-malyngolide in seven steps.



Scheme 33

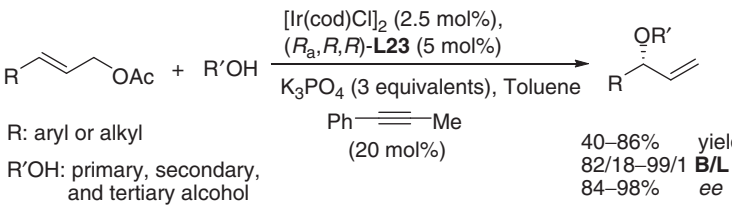
Chan reported a general palladium-catalyzed asymmetric allylic substitution of racemic 1,3-diphenyl allyl acetate with aliphatic alcohols in the presence of ligand **46** with excellent enantioselectivities (equation 110).[204] They observed an intriguing relationship between the enantioselectivity of the reaction and the electronic nature of the substituted benzylic alcohol. Higher enantioselectivity was observed when the benzylic alcohol contained an electron-rich *para*-substituent, and the selectivity diminished gradually as the substituent became more electron deficient. The aromatic electronic effect can be represented by the Hammett relationship. The Hammett plot of log(ratio of enantiomers) against σ_p showed a linear free-energy relationship ($\rho = -0.77$, $\gamma = 0.975$) between enantioselectivity and the electronic character of the substituent.



(110)

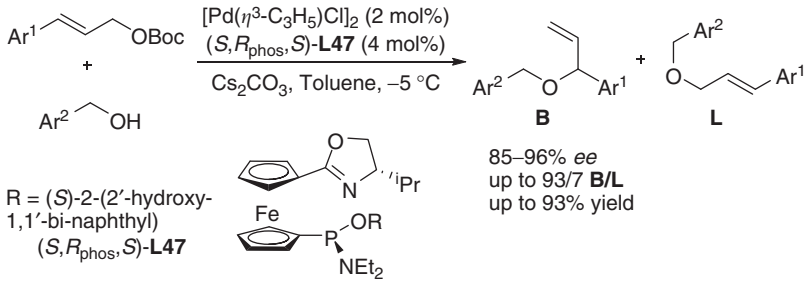
Ueno and Hartwig reported that primary, secondary, and tertiary alcohols, as well as silanols, participated directly in catalytic asymmetric allylic substitution by utilizing K_3PO_4 as the base (equation 111).[205] The AAA reaction with a metallacyclic iridium catalyst gave chiral, branched allylic ethers and silyl ethers in high yield and high enantioselectivity. The use of 20 mol% of

1-phenyl-1-propyne was necessary to suppress olefin isomerization that provide vinyl ether side product. It is notable that tertiary alcohols also reacted well with high enantioselectivity. Similarly, a planar chiral Ru-complex was also effective in the allylic etherification between allylic chlorides and MeOH or BnOH utilizing K_2CO_3 as the base.[206]



(111)

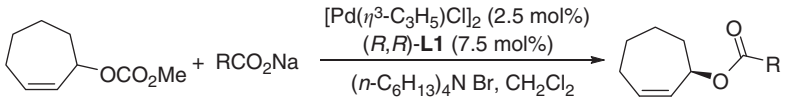
Hou and coworker revealed an unusual regio- and enantioselective Pd-catalyzed allylic substitution reaction of mono-substituted allylic substrates with substituted benzyl alcohols, affording the corresponding products in high regio- (up to 93/7 b/l ratio) and enantioselectivities (up to 96% *ee*) (equation 112).[207]



(112)

4.11.4.3 Carboxylate Nucleophiles

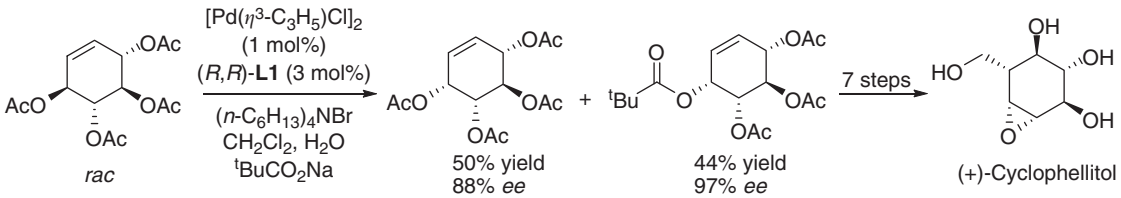
The use of carboxylates as oxygen nucleophiles in AAA reaction has less been explored, which may attribute to the product, allyl ester being also an electrophile for the reaction. To overcome racemization of the product, the reaction rate of the AAA with the starting ester must be faster than that of product ester. Trost and Organ demonstrated that the methyl cycloheptenyl carbonate can be deracemized to form the corresponding pivalate, isobutyrate, or propionate in excellent yields and enantioselectivities (equation 113).[208] The success of the reaction relies on the facile ionization of carbonate leaving groups, whereas the relatively electron-rich carboxylates is reluctant to ionize. It is necessary to monitor the reaction and temperature to prevent racemization of the product.



a) R = C(Me)3, 76% yield, 98% *ee*
b) R=CH(Me)2, 94% yield, 94% *ee*
c) R = Et, 91% yield, 98% *ee*

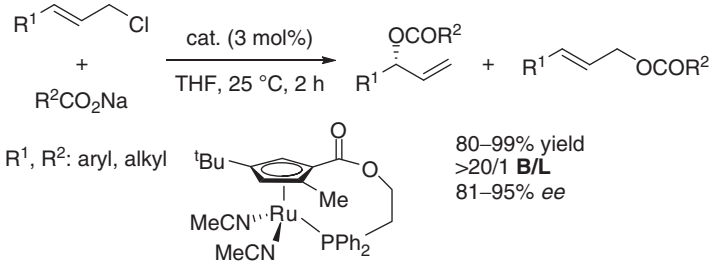
(113)

Trost and Hembre reported an asymmetric palladium-catalyzed kinetic resolution of racemic conduritol B tetraacetate with sodium pivalate as a useful carboxylate nucleophile with near perfect selectivity (Scheme 34).[209] An effective synthesis of the glycosidase inhibitor (+)-cyclophellitol illustrates the utility of this method.



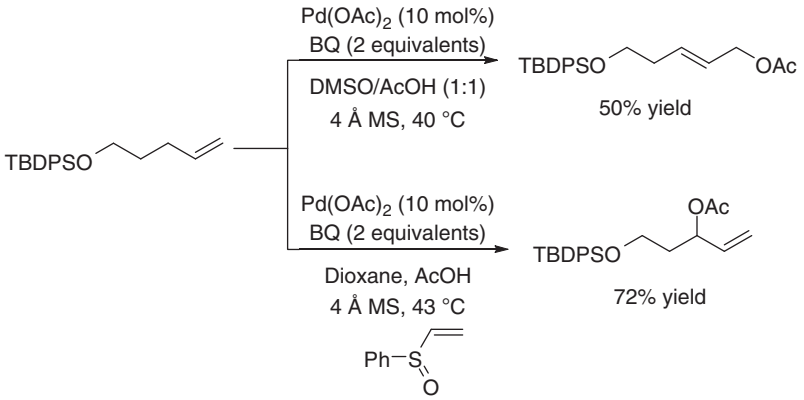
Scheme 34

The planar chiral Ru-complex proved to be an efficient catalyst for AAA reactions using sodium carboxylate as the nucleophile (equation 114).[210] Both aryl and alkyl allylic chlorides and aryl and alkyl carboxylate nucleophiles were employed in this reaction with excellent results. Notably, allylic chlorides performed more efficiently than allylic bromides (reduced *ee*) or allylic carbonates (no reaction), and sodium carboxylates are more efficient relative to other alkali metal carboxylates.



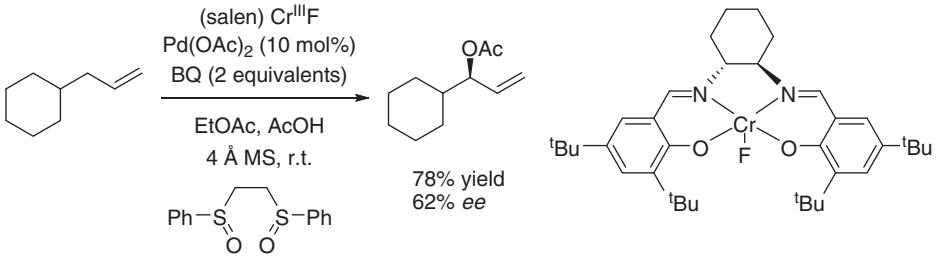
(114)

The allylic substitution of carboxylate could occur at allylic C–H position using a Pd(II)/BQ catalytic system (Scheme 35).[211] The addition of DMSO is critical to suppress the Wacker oxidation via sulfoxide ligation to palladium. The reaction is proposed to proceed via a π-allyl intermediate to afford the linear (*E*)-allylic acetates with high regio- and stereoselectivity. Interestingly, when a phenyl vinyl sulfoxide was used as the ligand rather than DMSO, the reaction proceeded with dramatic switch of regioselectivity to form branched allylic ester with monosubstituted olefins as substrate. Mechanistic studies suggested that sulfoxide and vinyl moieties of ligand were essential for promoting the C–H activation. BQ was acting not only as oxidant but also as a π-acid to accelerate the reductive elimination.



Scheme 35

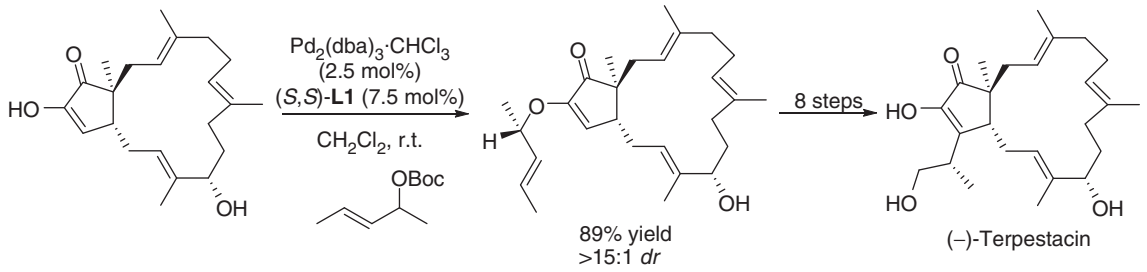
Following these results, Covell and White realized oxidative allylic acetoxylation of terminal olefins by introducing a chiral Lewis acid Cr(III)(salen) as cocatalyst (equation 115).[212] The branched allylic acetates were furnished with high regioselectivity and moderate enantioselectivity. The asymmetric induction possibly resulted from the coordination of Cr(III)(salen) with BQ. Thus the formed adduct of Cr(III)(salen)·BQ promoted the acetoxylation of π-allylpalladium complex to form enantioenriched branched allylic acetates.



(115)

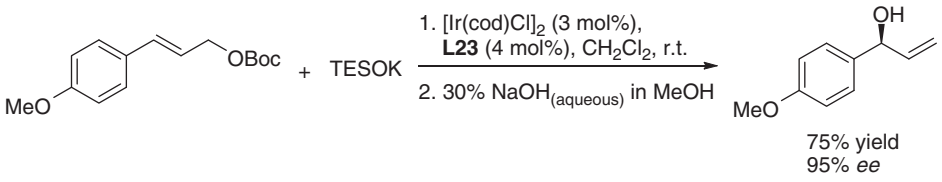
4.11.4.4 Other Oxygen Nucleophiles

3-Substituted cyclic 1,2-diketones exist as a single tautomeric structure. This conjugated enol is a useful nucleophile for AAA reactions. The *O*-alkylated products are preferentially formed in good yields and high enantiomeric excesses (Scheme 36).[213] These products readily take place by means of a Lewis acid-catalyzed Claisen rearrangements with high chirality transfer to give enantiomerically enriched *C*-alkylation products. Linear acyclic allylic carbonates and vinyl epoxides can also be used as electrophiles in these AAA reactions. This method has been successfully applied to the total synthesis of (–)-terpestacin.



Scheme 36

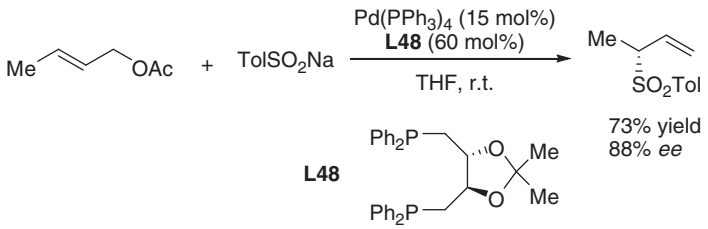
Silanols is a particularly attractive class of nucleophiles as an equivalent of hydroxide. Carreira and coworkers reported the first example of an iridium-catalyzed enantioselective allylation reaction of cinnamyl carbonate with potassium triethylsiloxide (TESOK), allowing convenient access to branched chiral allylic alcohol in excellent enantioselectivity (equation 116).[214]



(116)

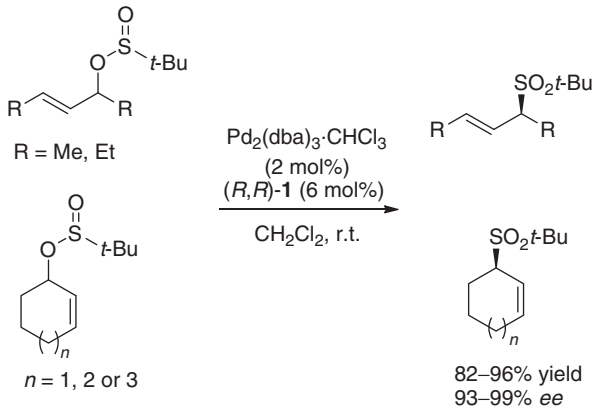
4.11.5 Sulfur Nucleophiles

A variety of sulfur derivatives, such as sulfones, thiocarboxylates, and thiols can be used as nucleophiles in transition metal-catalyzed allylic substitution reactions. The use of sulfones as nucleophile in AAA reactions has been successful by using a variety of catalytic systems. In 1986, Hiroi et al. reported an early example of Pd-catalyzed asymmetric sulfonylation of allylic acetate with sodium p-toluenesulfinate. The use of $Pd(PPh_3)_4$ in the presence of the chiral (−)-DIOP led to the formation of the allylic sulfone with 88% *ee* in 73% yield (equation 117).[215] Since then, many other types of allylic electrophiles including cyclic,[216] acyclic,[217] unsymmetrical,[30c] and gem-diacetate[218] were successfully used for such reactions.



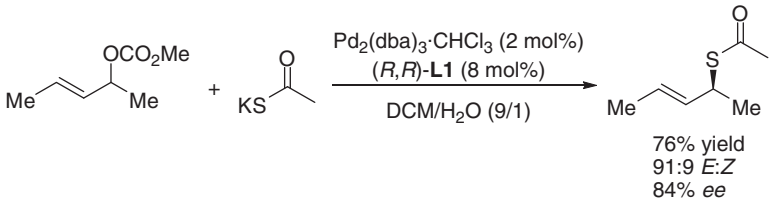
(117)

In 1986, Hiroi et al. reported 'internal nucleophiles' could be used to form chiral sulfones through the rearrangement of the chiral allylic sulphinates to chiral sulfones facilitated by catalytic amount of the palladium catalyst, thus avoiding the use of an external sulfone as the nucleophile.[219] Gais et al. demonstrated that racemic cyclic and acyclic allylic *S*-tolyl- and *S*-*tert*-butyl-sulfinates is rearranged to the corresponding isomeric allylic *S*-tolyl and *S*-*tert*-butyl sulfones with 93–99% *ee* in 82–96% yield in the presence of catalytic amounts of a chiral Pd/Trost ligand system (equation 118).[220]



(118)

Thiocarboxylates is capable to serve as a nucleophile for AAA reactions, which lead to the formation of synthetically useful chiral allylic thiocarbamates. Sinou demonstrated that potassium thioacetate could attack the allylic carbonates or acetates in the presence of a palladium(0)-complex to provide allylic thioacetates in good yields.[221] The reaction is regioselective with the formation of the less substituted allylic thioacetate. The Gais group reported that the palladium-catalyzed allylic alkylation of potassium ethanethioate with racemic cyclic and acyclic allylic esters using the Trost ligand gave the corresponding allylic thioesters with high *ee* values and yields (equation 119).[222] Palladium(0)-catalyzed enantioselective *O*,*S*-rearrangement of racemic *O*-allylic thiocarbamates is an alternative entry to chiral *S*-allylic thiocarbamates.[223]

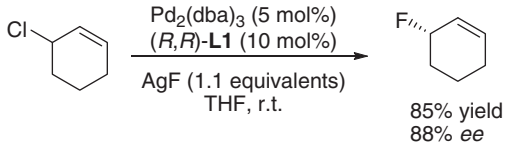


(119)

Reports on the use of thiols as nucleophiles are fewer. Gais has studied the formation of chiral allylic sulfides via palladium-catalyzed allylic substitution of allylic carbonate using thiol as the nucleophile.[217] The reaction required higher amounts of palladium catalyst as compared with those with sulfinate anions and was only applicable to 2-pyrimidinethiol, 2-pyridinethiol, and 4-chlorophenylthiol but not with *tert*-butylthiol. An equilibrium between a palladium thiolate complex and an π-allyl thiolate-ion pair could perhaps account for the higher catalyst loading.

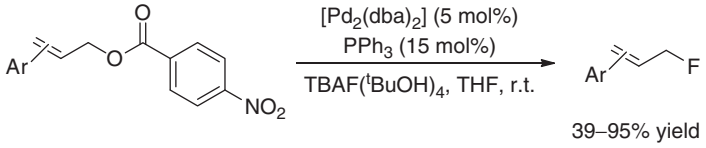
4.11.6 Fluorine Nucleophile

Allylic fluorides are key components of bioactive molecules and serve as versatile synthetic intermediates. The methods for C–F bond construction through allylic substitution had remained unexplored for long time. The use of the fluoride ion as the nucleophile requires overcoming several challenges, including the potential reversibility of the reaction and the low reactivity of solvated fluoride ion. In addition, the desolvated fluoride ion is a strong Brøsted base favoring elimination instead of substitution. The breakthrough work recently came from Katcher and Doyle (equation 120).[224] They found that a chiral bisphosphine-ligated palladium complex is competent for the enantioselective fluorination of cyclic allylic chlorides with AgF. Various cyclic allylic chlorides are suitable for the catalyst-controlled enantio-, diastereo-, and regioselective reaction. The stereochemistry of the reaction showed that the reaction may occur via an outer-sphere attack of fluoride on the allyl-Pd intermediate.

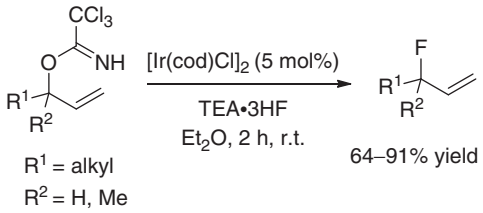


(120)

Brown, Gouverneur, and coworkers reported the synthesis of linear allylic fluorides by Pd-catalyzed nucleophilic substitution of allylic substrates with ammonium fluorides (equation 121).[225] The reaction regioselectively favored the formation of linear allyl fluoride. The judicious choice of allylic leaving group and the fluoride source is critical for the success of the reaction. Nguyen and coworkers reported an iridium-catalyzed allylic fluorination, which regioselectively favored the formation of branched secondary and tertiary allylic fluorides (equation 122).[226] Doyle and coworkers realized the highly branched-selective, asymmetric catalytic fluorination of acyclic allylic substrate with a chiral palladium catalyst.[227] The reaction is operationally trivial and displays well functional group tolerance.



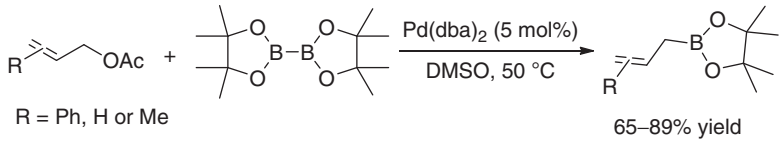
(121)



(122)

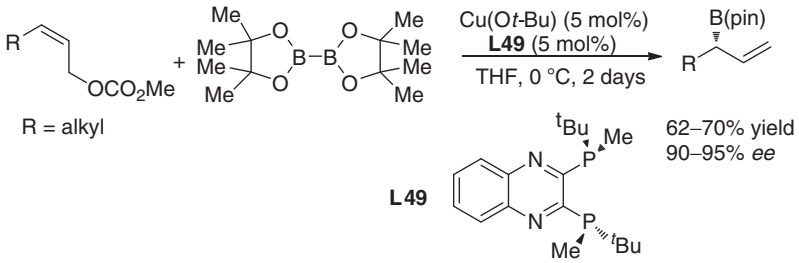
4.11.7 Boron Nucleophiles

Allylboron compounds are useful reagents in organic synthesis, especially for the stereoselective synthesis of homoallylic alcohols and amines. The cross-coupling of boryl nucleophile with allylic substrate is a convenient method for the synthesis of allylboron. Miyaura firstly demonstrated that the cross-coupling reaction of bis(pinacolato)diboron with allyl acetates was efficiently catalyzed by $Pd(dba)_2$ in DMSO at 50 °C (equation 123).[228] The reaction regio- and *E*-stereoselectively provided the pinacol esters of allylboronic acids in high yields. A platinum(0)-catalyst was proved efficient to catalyze the borylation of allyl halides with pinacolborane as the nucleophile.[229] Palladium pincer complex was capable to catalyze the reaction of vinyl cyclopropanes, vinyl aziridines, and allyl acetates with tetrahydroxydiboron.[230] The reactions only produced linear allylboronic acids. The resulting functionalized allylboronic acids were subsequently reacted with aqueous KHF_2 to afford the corresponding potassium trifluoro (allyl)borate derivatives in good to excellent yields. It was proposed that this reaction occurs without the formation of a (π-allyl) palladium(II)complex.



(123)

The employment of the xantphos-ligated Cu-O^{t}Bu catalyst resulted in γ-selective and stereospecific substitution reaction of allylic carbonates with bis(pinacolato)diboron as the nucleophile.[231a] It was proposed that the reaction likely proceeded through an S_N2' pathway with L*Cu–B(pin) as the reactive nucleophile rather than the standard AAA reaction mechanism. On the basis of the results, the same group developed an asymmetric borylation of allylic carbonates employing $B_2(pin)_2$ as the nucleophile under Cu-catalyzed conditions (equation 124).[231b] This formal AAA reaction allows access to enantiomerically enriched allylic boronates. However, only pure *cis* substrates gave excellent enantioselectivity, the *trans* substrates showed poor enantioselectivity. Racemic cyclic allylic alkyl ethers were also viable substrates for copper-catalyzed asymmetric allylic borylation with excellent selectivity.[231c] The Hoveyda group extended substrate scope of these allylic substitutions to trisubstituted allylic carbonates using chiral bidentate NHC–Cu complexes. Allylic boronates that bear a quaternary carbon center were provided with excellent enantioselectivity.[231d] The McQuade group used allylic aryl ether substrates for these allylic substitutions.[231e] Both the *E* and *Z* isomers gave the same absolute configuration with high *ee* and yield in the presence of a six-membered *N*-heterocyclic carbene (6-NHC)-Cu(I).



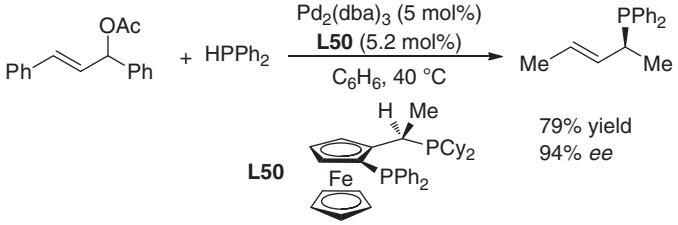
(124)

4.11.8 Other Nucleophiles

In addition to N, O, S and B, there have been reports of using other atoms as nucleophiles in AAA reactions. Among them, the most studied are hydride nucleophiles. Tsuji and Yamakawa first reported on the palladium-catalyzed reduction of allylic esters with formic acid to give less substituted olefins.[232] Mechanistic studies demonstrated that the olefin was formed by reductive elimination from the key intermediate, Pd(II)(π-allyl)(hydrido)(L), which was produced by the decarboxylation of the palladium formate complex. The use of monodentate phosphine ligand was essential to get high regioselectivity.[233] Following these results, Hayashi and coworkers developed a catalytic asymmetric reduction of allylic esters with formic acid using palladium-MOP complexes as catalyst.[234]

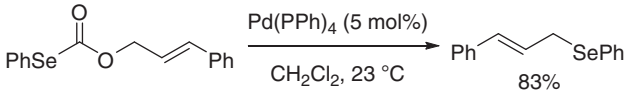
Allylic silanes have found wide application in synthetic methodology and total synthesis of complex molecule. The allylic substitutions employing silyl cuprates as nucleophile are well established.[235a–d] These protocols require stoichiometric amounts of copper to generate silicon–copper reagents. Oestreich and Auer reported the first copper-catalyzed allylic substitution reactions of allylic acetates and carbamates employing a bis(triorganosilyl)zinc reagent.[235e] The regioselective synthesis of branched allylic silanes from linear allylic substrate was also feasible through copper-catalyzed direct C–Si bond formation.[235f,g] Hayashi and coworkers have observed that the reaction of optically active π-allylpalladium complexes with $Cl_3SiSiMe_3$ or $Cl_2PhSiSiMe_3$ in the presence of triphenylphosphine proceeded with retention of configuration to give optically active allylsilanes in high yields.[235h] The catalytic asymmetric allylic silylation was accomplished by means of a chiral catalyst with moderate enantioselectivity.[235i]

The report on using phosphine nucleophile for transition metal-catalyzed reaction is rare mainly because the resulting phosphine product could coordinate the metal and thus deactivates the catalyst. In 1983, Fiaud found that $Pd(PPh_3)_4$ catalyzed the reaction of lithium diphenylthiophosphides with allylic acetate to furnish the allylic diphenylphosphine sulfides in high yields. However, the reaction of lithium diphenylphosphide gave only limited yield (<15%).[236] Togni and coworkers provided an example of Pd-catalyzed enantioselective allylic substitution reactions with secondary phosphines as nucleophiles. The new chiral allylic phosphine was obtained in good yield and 94% *ee* using Josiphos as the chiral ligand and 1,3-diphenylallyl acetate as substrate. However, the substrate scope of the reaction is very narrow (equation 125).[237]



(125)

Allylic selenides are versatile intermediates in organic synthesis, which could be used as a synthon of allylic anion stabilized by seleno group and be regioselectively α-alkylated. In 1990, Sakai and coworkers reported that allylic phenyl selenides could be prepared from the reaction of allylic acetate and diphenyl diselenide with the aid of SmI_2 in the presence of a palladium catalyst under mild conditions.[238] The reaction may proceed through the polarity inversion of electrophilic π-allylpalladium complexes to nucleophilic species with the aid of SmI_2, which then trap electrophiles. Waetzig and Tunge demonstrated that palladium facilitated decarboxylative coupling of easily accessible allylic seleno carbonates to give allylic selenides in moderate to excellent yields (equation 126).[239] Mechanistic studies suggest that the decarboxylative allylation occurs via an outer-sphere mechanism, giving products with retention of stereochemistry. Employment of a chiral palladium catalyst leads to the kinetic resolution of selenocarbonates to provide both the allyl selenide and selenocarbonate in high enantioselectivities.



(126)

4.11.9 Conclusion

In the past two decades, the field of the reactions of nucleophile with allyl metal complex has witnessed tremendous advancement. Especially, the transition metal-catalyzed asymmetric allylic substitution reaction has become a powerful synthetic tool in organic chemistry. To date a wide variety of nucleophiles including carbon and heteroatom nucleophiles have been successfully employed in such reaction. The chemo-, regio-, and enantioselectivity can be controlled in the formation of a variety of C–C and C–X bonds through the judicious choice of metal, chiral ligands, and reaction additives. The power of these reactions has been demonstrated in the total synthesis of natural products and chiral drugs as key steps. Compared with carbon nucleophiles, the use of heteroatom nucleophiles in the reaction with allyl metal complex falls far behind. Some nucleophiles remain largely unexplored. Some intriguing results appeared with fluorine nucleophiles. Silicon and phosphine nucleophiles have found some interesting success. The use of allylic alcohols or simple alkenes as precursors of allyl metal complex remains a challenge, although some encouraging reports have appeared. Continual progress in this fascinating area, with particular emphasis on substrate scope and catalyst efficiency will enable this methodology to be an even more reliable tool in organic synthesis.

Acknowledgment

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4.12 Radical Addition Reactions

H Subramanian, North Dakota State University, Fargo, ND, USA
Y Landais, Université Bordeaux-1, Talence Cedex, France
MP Sibi, North Dakota State University, Fargo, ND, USA

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Glossary

Addition reaction A class of organic reaction that is limited to molecules containing multiple bonds. Other molecules add across the multiple bonds to form an adduct.

Allylic strain (A strain) The *van der waals* repulsion between the substituents on the double bond and those in an allylic position that cause the destabilization of a conformation.

Chiral auxiliary A covalently attached chiral molecule that is capable of making the enantiotopic faces of the organic substrate diastereotopic. Chiral auxiliaries should be easily removed after the reaction.

Free radical An atom or a molecule or an ion with an unpaired electron is termed as a free radical. The presence of these unpaired electrons generally make them highly reactive.

Organocatalysis A form of catalysis, wherein simple organic molecules (termed as organocatalysts) increase the rate of chemical reactions.

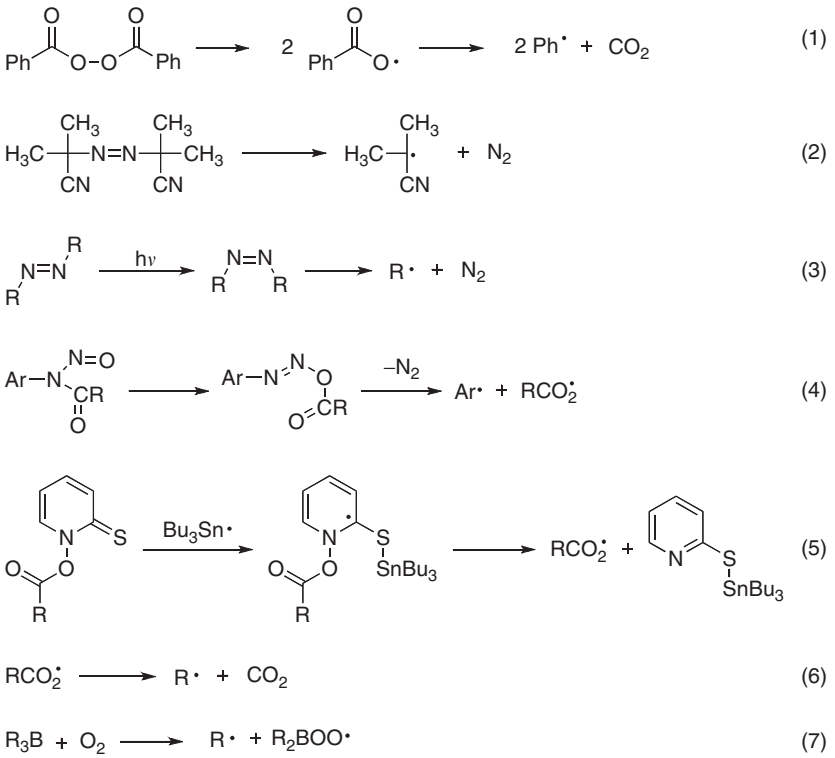
Stereoselective reaction A chemical reaction where there is a preference for one stereoisomer over the other. These are further classified to diastereoselective and enantioselective reactions.

4.12.1 Introduction

An atom or a molecule or an ion with an unpaired electron is termed as a free radical.[1–3] The presence of these unpaired electrons generally make them highly reactive. In order to generate free radicals, a covalent bond must undergo homolysis. This kind of cleavage results in the formation of two fragments containing unpaired electrons. The homolytic cleavage to free radicals can be achieved by a physical or chemical process. The physical method of generating radicals involves the application of heat or light energy to the substrates and the chemical method involves the use of substances known as radical initiators. These are substances that are generally stable at room temperature but are prone to homolytic cleavage under mild reaction conditions (Scheme 1).

A few methods of generating free radicals are discussed below:[4]

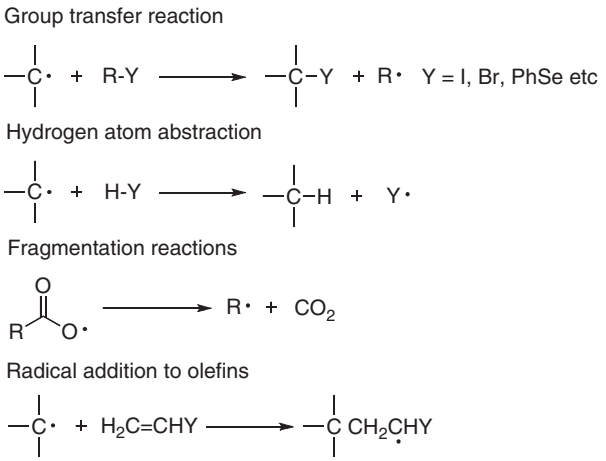
1. The weak O–O bond in peroxides ($\sim$30–45 kcal mol^{-1}) makes it a suitable candidate for radical initiation process (equation 1, Scheme 1). The O–O bond can be cleaved homolytically under mild thermal or photolytic conditions to generate radicals. The most commonly used peroxides include benzoylperoxide, *tert*-butylhydroperoxide, di-*tert*-butylperoxide and *tert*-butylperoxybenzoate.



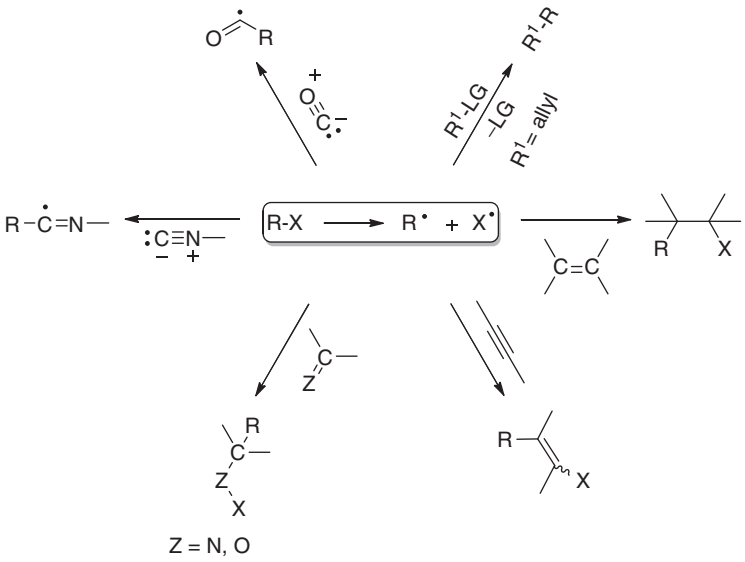
Scheme 1 Methods of radical generation.

2. Other source for radicals are azo compounds. Similar to peroxides, radicals from azo compounds can be generated thermally or photochemically. The decomposition temperatures of the azo compounds depend on the N-substituents. Compounds with an electron-withdrawing substituent that stabilizes the resultant radical decompose with ease, and hence AIBN (azoisobutyronitrile) is commonly used as a radical initiator (equation 2, **Scheme 1**). During photolysis, the *trans* azo compounds are converted to the *cis*-isomer and the *cis*-isomer decomposes to furnish radicals (equation 3, **Scheme 1**). *N*-Nitrosoanilides are also used as radical initiators and the radical generation proceeds by a similar mechanism to that of azo compounds: decomposes to nitrogen, acyloxy, and aryl radicals (equation 4, **Scheme 1**).[5,6]
3. Esters of *N*-hydroxy-2-thiopyridone are also an excellent source of radicals. The tributyltin radical adds to sulfur of the thiocarbonyl group and the resulting intermediate decomposes to give acyloxy radical which then decarboxylates to give a carbon-centered radical (equations 5 and 6, **Scheme 1**).[7]
4. Interestingly, several reagents such as organoboranes have been used as source of radicals in several organic transformations.[8] The simplest system involves the use of triethylborane (Et_3B/O_2) as the radical initiator (equation 7). This initiator can be used at low temperatures (−78 °C).

Free radicals can undergo several types of basic reactions: (1) atom or group-transfer reaction, where an atom or group is transferred to the radical formed during the reaction. An important reaction of this kind is the hydrogen atom abstraction reaction (**Scheme 2**). (2) The radicals can also eliminate a neutral molecule, for instance CO_2 to furnish another radical that can readily be functionalized. Such reactions are called as fragmentation reactions. (3) Another basic type of reaction that a radical undergoes is an addition reaction. Unlike the simple hydrogen atom-transfer processes, these reactions result in the formation of new carbon–carbon bonds. In **Scheme 2**, a simple intermolecular radical addition to an alkene to give an intermediate radical is shown. The addition reactions are also classified according to the nature of substrates to which the radical is added. Free-radical additions to several substrates are shown in **Scheme 3**. The addition reactions can be classified into two types: radical additions to carbon–carbon and carbon–heteroatom multiple bonds. Within each class, the addition could be further classified into intramolecular and intermolecular additions, depending on whether the addition takes place within the same molecule or to a different molecule. Although both intermolecular as well as intramolecular radical additions are known, the focus of the current review is restricted to intermolecular processes only. The readers should consult the following reviews for details on intramolecular process.[9–11] The review is divided into two parts: (1) radical additions to carbon–carbon multiple bonds and (2) radical additions to carbon–heteroatom multiple bonds.



Scheme 2 Types of radical reactions.



Scheme 3 Free radical additions to different substrates.

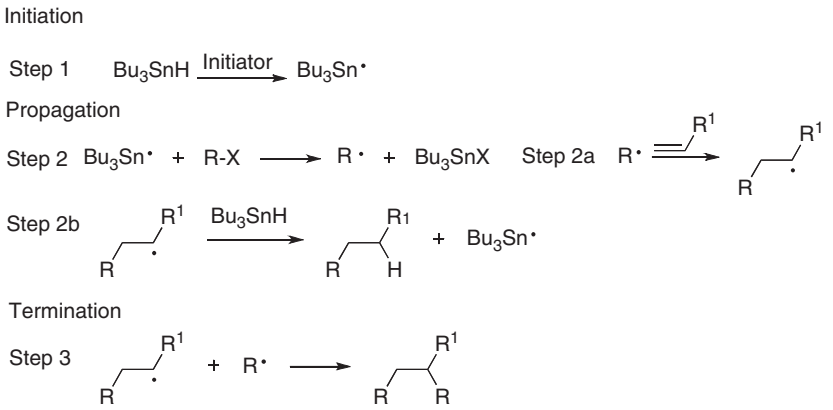
4.12.2 Free-Radical Addition to Carbon–Carbon Multiple Bonds

4.12.2.1 Addition to Carbon–Carbon Double Bonds

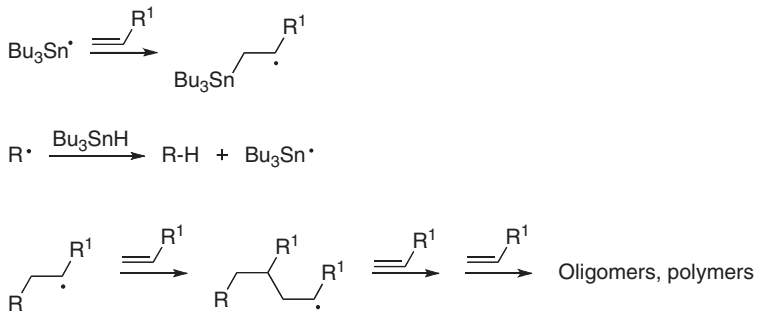
A radical chain mechanism for intermolecular free-radical addition to a simple alkene is shown in Scheme 4. The tributyltin radical generated in the initiation step reacts with other precursors to form carbon-centered radicals (R). These radicals add to nonradical species (alkenes) resulting in an intermediate radical that reacts with tributyltin hydride to generate the desired product and tributyltin radical, which again enters the propagation chain. One of the ways by which the chain is terminated is by recombination of two radicals as shown.

Although the depicted mechanism shows the formation of the desired product, the radical additions are often plagued by several competing side reactions, some of which are shown in Scheme 5. Instead of generating the R, the tributylstannyl radical can add to alkenes. Another important side reaction is the premature reduction of R. Lowering the concentration of stannane and increasing the concentration of olefin to increase the formation of the desired product could avoid the unwanted reduction. But increased concentration of alkene would result in the formation of oligomers and polymers. So, it is very important to consider these side reactions while attempting to design a synthesis based on free-radical additions.

An important criterion for radical addition is the matching of complementary polarity of the reacting partners (radical and the alkene).[12] Hence a nucleophilic radical will react with an electron-deficient olefin and an electron-rich olefin will react with

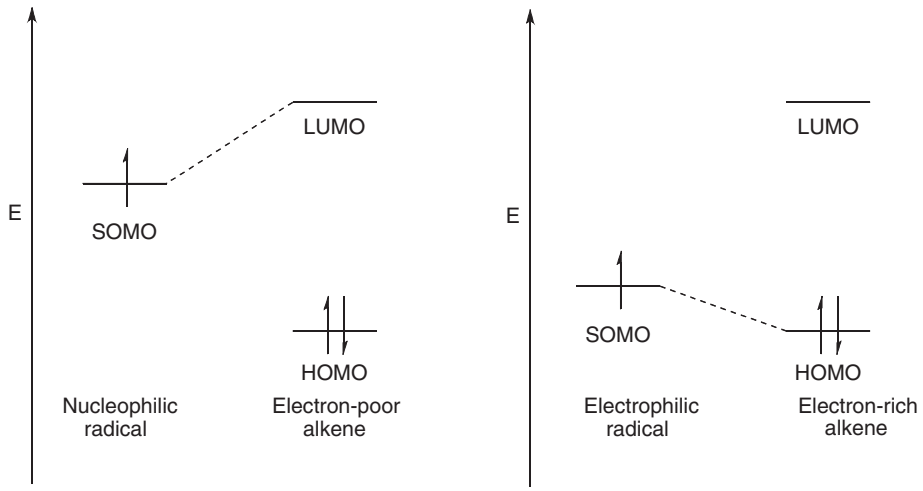


Scheme 4 Chain mechanism for radical addition to simple olefins.

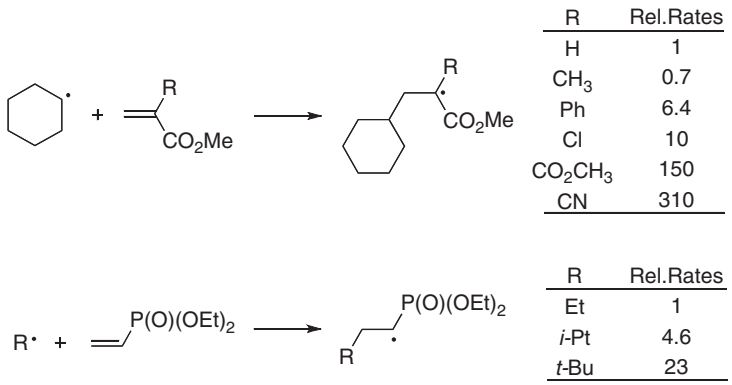


Scheme 5 Side reactions competing with desired radical additions to olefins.

electrophilic radical. This can be explained on the basis of orbital interactions of singly occupied molecular orbital (SOMO) of the radicals with lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) of alkenes. Nucleophilic radicals have high-lying SOMO orbitals and SOMO–LUMO interactions are the most important (Scheme 6). Hence an increase in SOMO energy of the radical or the lowering of LUMO energy of alkene would favor such radical additions between nucleophilic radicals and electron-deficient alkenes. For instance, cyclohexyl radicals add to methyl acrylates. There is a substantial rate enhancement in changing the substituent from methyl to a cyano group (Scheme 7).[13] Similarly, there is a 20-fold rate enhancement in adding *tert*-butyl radicals to vinylphosphonates when compared to the addition of ethyl radical (Scheme 7).



Scheme 6 Polarity matching in radical additions.

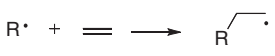


R	Rel.Rates
H	1
CH_3	0.7
Ph	6.4
Cl	10
CO_2CH_3	150
CN	310

R	Rel.Rates
Et	1
i-Pt	4.6
t-Bu	23

Scheme 7 Addition of nucleophilic radicals to electron-poor alkenes.

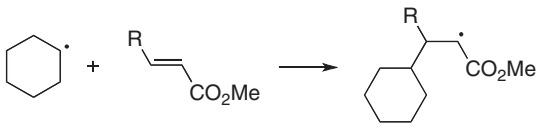
The electrophilic radicals have low-lying SOMO orbitals. In this case the SOMO–HOMO interactions become more important. Hence electrophilic radicals add efficiently to electron-rich alkenes. For instance, CF_3 radicals add 100 times faster to ethylene when compared to ethyl radicals (Scheme 8).[14]



R	Rel.Rates
Et	1
CH_2F	8
CF_3	100

Scheme 8 Addition of electrophilic radicals to electron-rich alkenes.

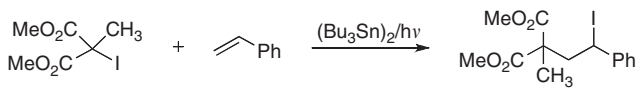
Since most radical reactions are characterized by early transition states, the size of the radicals has little effect on the reaction rates and hence tertiary radicals add effectively to form quaternary carbons. In contrast, the substituents on the olefinic trap retard the rate of the radical additions. For example, addition of cyclohexyl radicals is retarded by β-substitution on the acrylates (Scheme 9).



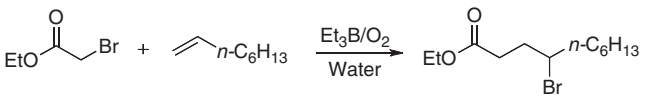
R	Rel.Rates
H	1000
CH_3	11
t-Bu	.05

Scheme 9 Effect of substituents on rate of radical addition.

Since its discovery in 1940s by Kharasch,[15,16] atom-transfer radical addition reactions (ATRA) have become an important process for the simultaneous formation of C–C and C–X bonds. Since then, Oshima,[17,18] and Curran[19–21] have developed ATRA into a useful reaction in synthetic organic chemistry. In an early example, Curran and coworkers reported the bis(tributyl)tin-mediated halogen atom-transfer reaction (Scheme 10). Electrophilic radicals generated from iodomalonates were added to several different inactivated alkenes. The reactions were chemically efficient. The authors also demonstrated the synthetic utility of such ATRA adducts. In another example, Oshima et al. reported triethylborane-mediated bromine atom transfer to 1-octene using α-bromo carbonyl compounds as radical precursors (Scheme 11).[22]



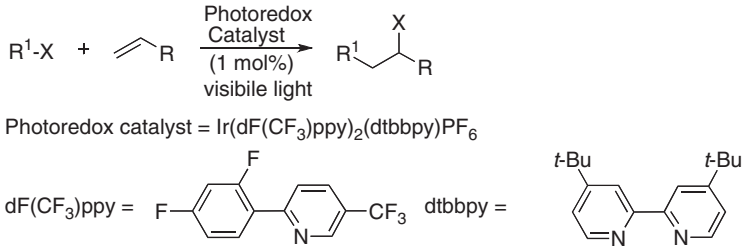
Scheme 10 Iodine atom transfer to alkenes.



Scheme 11 Triethylborane-mediated bromine atom-transfer reaction in water.

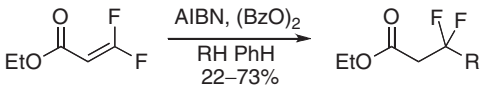
These reactions were efficient in water and polar organic solvents such as *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) when compared to nonpolar organic solvents. Computational studies revealed that polar solvents lower the transition state energies for the radical addition step and the bromine atom-transfer step. It is also proposed that in protic solvents, the coordination of carbonyl group to the proton is responsible for effective propagation. Group-transfer reactions with selenium[23–26] and tellurium[27,28] are also well known.

Recently, Stephenson and coworkers have disclosed a protocol for effective ATRAs under mild photolytic conditions using oxidative quenching of photoredox catalysts (Scheme 12).[29,30] The reactions were characterized by very high chemical yields, mild conditions, high functional group tolerance, and low catalytic loading ($\sim$1.0 mol%). The authors also established the synthetic utility of such ATRA adducts. This protocol can be used to introduce vinyl trifluoromethyl to olefins.



Scheme 12 ATRAs using visible light photoredox catalysis.

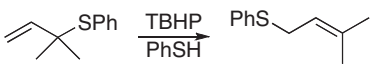
Bumgardner and coworkers reported the addition of nucleophilic radicals to β,β-difluoroacrylates (Scheme 13).[31] Conventional Michael-type nucleophilic additions were plagued by elimination of fluoride. Alkoxy and acyl radicals were added with ease. The reactions were successful in the presence of a combination of AIBN and benzoylperoxide initiators.



RH = tetrahydrofuran, 1,3-dioxolane, benzaldehyde, hexanal

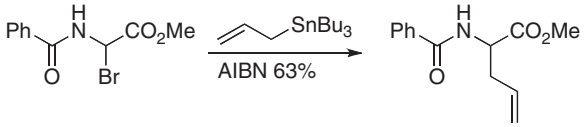
Scheme 13 Radical conjugate additions to fluorinated acrylates.

Lewis and Winstein reported the first radical-mediated fragmentation reaction. α,α-Dimethylallyl phenyl sulfide on treatment with thiophenol in presence of TBHP (*tert*-butyl hydroperoxide) gave an isomeric compound γ,γ-dimethylallyl phenyl sulfide (Scheme 14).[32] The reaction is proposed to proceed via the initial addition of thiophenoxy radical to the alkene, followed by the fragmentation of the resultant radical to form the product.



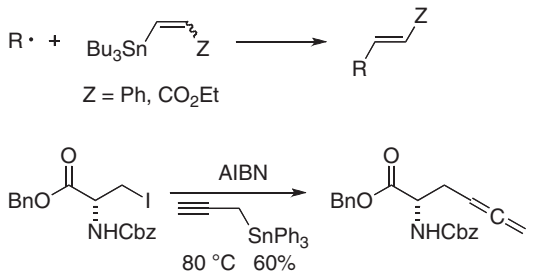
Scheme 14 Fragmentation of allyl sulfide.

This kind of radical addition followed by fragmentation is often used for allylation of carbon-centered radicals. Allyltributyltin is the most commonly used reagent for allylation of carbon-centered radical. Easton et al. have shown that glycine derivative could undergo effective allylation in the presence of AIBN. This provides a platform for the synthesis of unnatural amino acids (Scheme 15).[33]



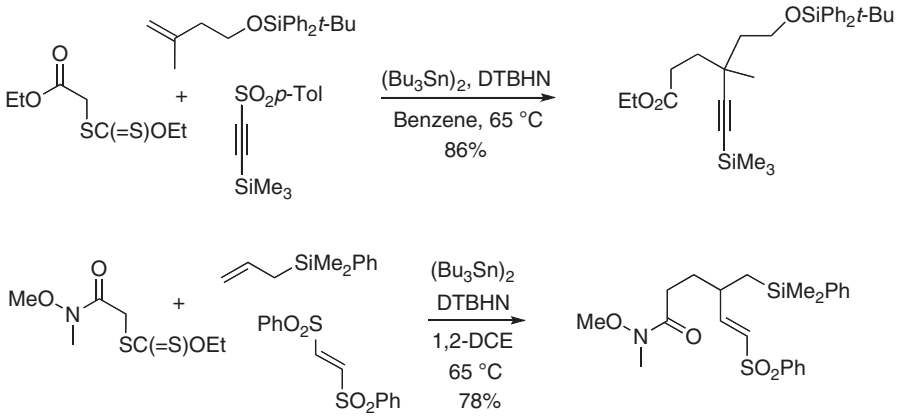
Scheme 15 Allylation of glycine derivative.

Russell et al. reported the first protocol for the vinylation of alkyl halides. The alkyl radical generated from corresponding alkyl halides add to the carbon atom of the alkene attached to tributyltin moiety. The resultant radical then undergoes fragmentation to give alkenes (Scheme 16).[34] In order to direct the radical addition to the carbon attached to tin, there should be an electron-withdrawing group at carbon β to the tributyltin. Baldwin et al. reported that propargyl stannane could be employed efficiently in the synthesis of functionalized allenes (Scheme 16).[35]



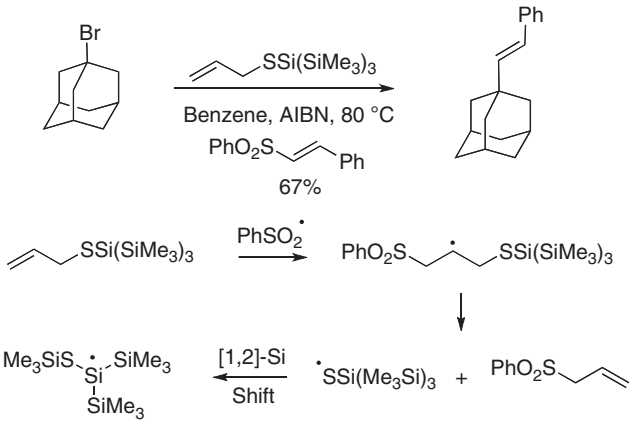
Scheme 16 Vinylation and allenation of alkyl radicals.

Landais and coworkers developed a three-component process involving, as a last elementary step, a vinylation or an alkynylation of a nucleophilic radical generated through the addition of an electron-poor radical onto an olefin (Scheme 17).[36] Vinyl and alkynylsulfones were used for the reaction, affording good yields of the desired carbo-vinylation, and carbo-alkynylation products.



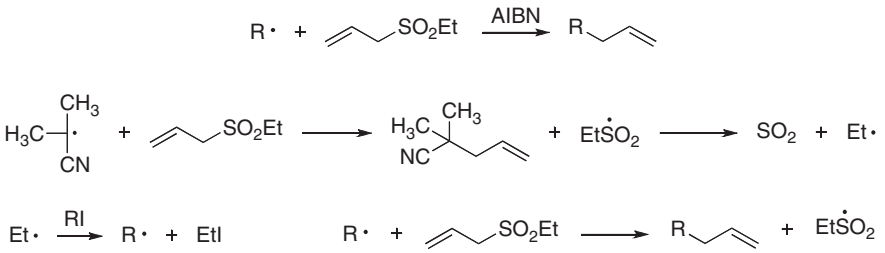
Scheme 17 Carbo-vinylation and alkynylations of olefins.

Tin-free vinylation, oximation, and allylation of alkyl halides were developed by Landais et al., relying on the known fast addition of phenylsulfonyl radicals onto olefins including allylsilanes and allylthioethers.[37] For instance, adamantyl bromide was converted into the desired olefin after reaction with a mixture of a vinylsulfone and tristrimethylsilyl allylthioether (Scheme 18). The latter, on reaction with the phenylsulfonyl radical provides, after fragmentation, a thiyl radical, which rearranges through a [1,2]-silyl shift into a silyl radical which can propagate the radical chain.



Scheme 18 Carbo-vinylation and alkynylations of olefins.

Zard showed that alkyl radical can be allylated using allylsulfones as the allylating agent (Scheme 19).[38] The proposed chain propagation begins by the addition of isobutyryl radical addition to the sulfone. The resulting ethyl sulfonyl radical extrudes SO_2 to form ethyl radical. Ethyl radical abstracts iodine atom from the alkyl iodide to form alkyl radical, which then adds to allylethyl sulfone to form the product. The authors have demonstrated that the protocol is applicable to a wide range of substrates with high chemical efficiency.



Scheme 19 Allylation using sulfones.

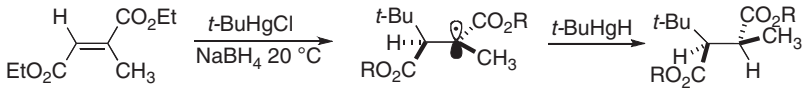
4.12.2.1.1 Diastereoselective radical additions to carbon–carbon double bonds

Unlike ionic reactions, radical reactions are carried out under mild neutral conditions. This prevents the use of harsh acidic or basic conditions that can promote epimerization or decomposition of the product. Since radical reaction conditions are mild, they are compatible with a variety of functional groups and often avoid the need for protection/deprotection of functional groups. Although radical reactions are well known, it is only after 1990s, the literature has seen an outburst in the number of stereoselective radical reactions. Several reviews on various synthetic and stereochemical aspects of radical chemistry have been published in the last two decades.[39–41]

Diastereoselectivity in radical reactions can be controlled by two approaches: (1) substrate-controlled approach and (2) chiral auxiliary-controlled approach. Although it is easy to control relative stereochemistry in cyclic systems, it is more difficult to establish stereocontrol in acyclic counterparts. In the 1980s, scientists attributed high reactivity and flexibility of acyclic radicals as reasons for failure to achieve highly stereoselective reactions. But in the 1990s, Porter, Giese, and Curran established several ways of achieving stereocontrol in acyclic systems.[42] Since then, synthetic chemists have been successful in controlling relative as well as absolute stereochemistry in radical reactions.[40]

4.12.2.1.1.1 Substrate-controlled radical additions

Hart[43,44] and Giese[45] demonstrated that the concept of allylic strain could be used to control 1,2-stereoselection. Giese reported the reductive alkyl radical addition to α,β-unsaturated esters (Scheme 20). Very high diastereoselectivity (27:1) was obtained in the reaction. This high diastereoselectivity could be explained on the basis of allylic strain: the radical formed during the reaction is a planar allylic-type radical and in order to avoid allylic strain the radical adopts a conformation in which the C–H bond adjacent to the radical points in the same direction as the carbonyl group of the ester and eclipses the double bond of the enoyl radical. In this conformation, the bulky *tert*-butyl group shields one face of the plane so that hydrogen abstraction can take place from the face opposite to *t*-Bu group. Hence the reaction in Scheme 20 shows a preference for *anti* product.

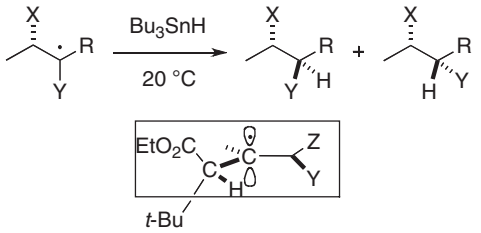


Scheme 20 Diastereoselective hydrogen abstraction.

Curran,[46] Giese,[47] and Renaud[48] demonstrated that substituents at the radical center can also induce diastereoselectivity. In order to attain preferred conformation devoid of any allylic strain, the substituent on the radical center must be in conjugation with the *p*-orbital of the radical. When the substituent is Csp^2 the observed stereoselectivity is high. But for substituent such as CN no selectivity is observed (Scheme 21).

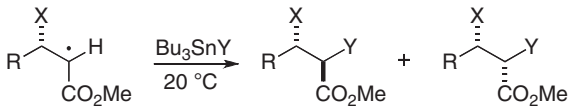
Using different radical traps, a similar trend in diastereoselectivity was observed. The diastereoselectivity depends on the size of the alkyl group attached to the carbon adjacent to the radical center and also the source of the radical trap. From Scheme 22 it is evident that the use of allyl stannane as radical trap gave better diastereoselectivity. Also the steric size of the carbon adjacent to the radical center also dictates the stereoselectivity. With smaller methyl substituent, the shielding is not effective and the hydrogen abstraction can take place from either face resulting in reduced diastereoselectivity.[49,50]

Giese and coworkers reported the addition of alkyl radicals to α-methylene-δ-lactones (Scheme 23).[51] They found that increasing the bulk of the alkyl radicals in conjugate additions to unsaturated lactones could increase the diastereoselectivity in



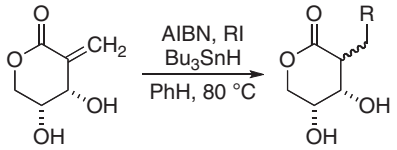
X	Y	R	*syn:anti*
OTBDPS	CO_2Me	CH_2-*t*-Bu	1:30
OTBDPS	Ph	Me	1:10
Bn	Bn	CH_2*t*-Bu	1:6
OTBDPS	CN	CH_2*t*-Bu	1:1
OTBDPS	TTMS	CH_2*t*-Bu	4:1

Scheme 21 Effect of α-substituent on the stereoselectivity of the reaction.



X	R	*syn:anti*	
		Bu_3Sn-D	Bu_3Snallyl
t-Bu	Me	7:1	16:1
$PhMe_2Si$	Me	9:1	4.5:1
Ph	Me	1:1.4	1:2.8
Ph	OMe	4:1	17:1

Scheme 22 Diastereoselective hydrogen abstraction and allylation.

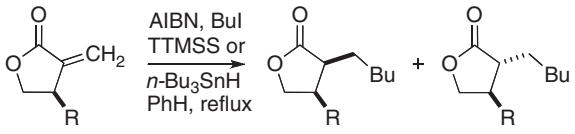


R = *n*-C_6H_{13}; 65% Yield; *cis:trans* = 2:3
R = *t*-Bu; 50% Yield; *cis:trans* = 5.7:1

Scheme 23 Steric effect on diastereoselectivity in radical reactions.

hydrogen atom abstraction. Hence, from Scheme 23 it is clear that on going from primary to tertiary alkyl radicals, the selectivity also increased toward the product where H-abstraction takes place *cis* to the neighboring hydroxyl group.

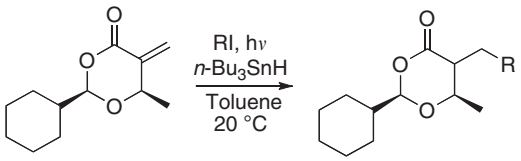
Sato et al. reported the addition of nucleophilic alkyl radicals to α-methylene-γ-lactones (Scheme 24).[52] The selectivities obtained during these studies were modest. By changing the nature of the H-atom transfer reagent, the diastereoselectivity established during the hydrogen abstraction step could be reversed. When tristrimethylsilyl silane was used as the hydrogen source, there is selectivity for the *cis*-product. In contrast, tributyltin hydride in the presence of a bulky Lewis acid furnished the *trans* product as the major isomer.



R = Ph 60%, *dr* = 66:34
R = *c*-Hexyl, 65%, *dr* = 24:76

Scheme 24 Intermolecular radical additions to unsaturated lactones.

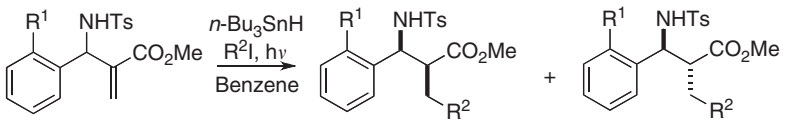
Giese and coworkers examined the addition of nucleophilic alkyl radicals to methylidene dioxanones (Scheme 25).[53] The selectivity for the resultant *trans* product was >50:1 and the size of the radical had no impact on stereoselectivity.

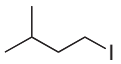


R	Yield	*threo/erythro*
t-Bu	97	>50:1
Cyclohexyl	71	>50:1
Octyl	49	>50:1

Scheme 25 Diastereoselective radical additions to methylidene dioxanones.

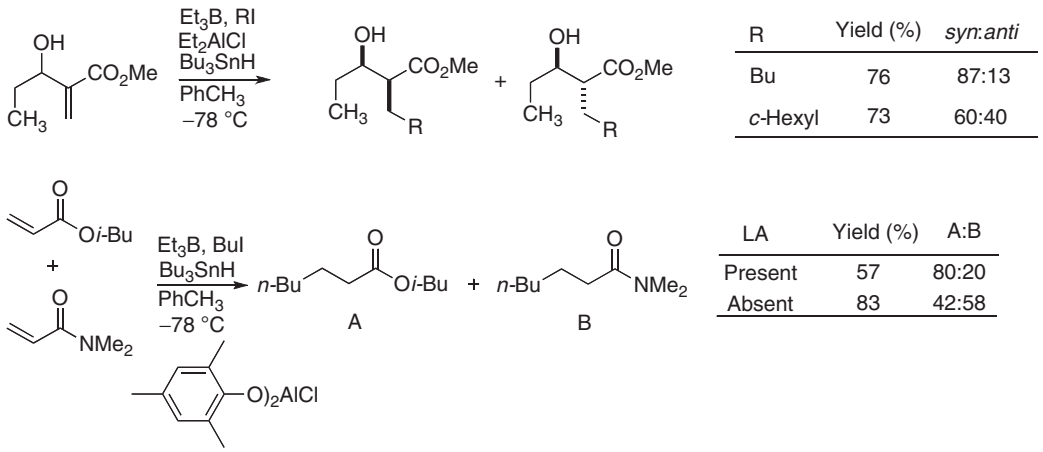
Kundig and coworkers observed high 1,2-stereoinduction during the addition of alkyl radicals to α-substituted acrylates (Scheme 26).[54] With the increase in the radical bulk, the selectivity decreased. The diastereoselectivity in this reaction was attributed to intramolecular hydrogen bonding between the sulfonamide hydrogen and the carbonyl group.



R^1	R^2I	Yield	*syn*:*anti*
Me		84	12:1
OMe	*t*-BuI	89	1.1:1

Scheme 26 1,2-Stereoinduction in conjugate radical addition.

Lewis acid additives play an important role in intermolecular radical additions. Sato and coworkers reported that radical addition to hydroxy acrylate proceeds with high selectivity when primary radicals are employed (Scheme 27).[55] The observed selectivity was attributed to a six-membered chelate formed between the Lewis acid and the acrylate. But when competition experiments were performed using enoates and amides, the radicals added chemoselectively to the amide substrates. The increased reactivity of amides compared to esters was attributed to the selective Lewis acid complexation with amides and hence the enhancement in the reactivity of amides.

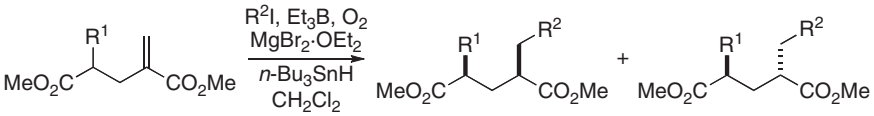


R	Yield (%)	*syn*:*anti*
Bu	76	87:13
c-Hexyl	73	60:40

LA	Yield (%)	A:B
Present	57	80:20
Absent	83	42:58

Scheme 27 Dual role for Lewis acid-catalysts in conjugate addition.

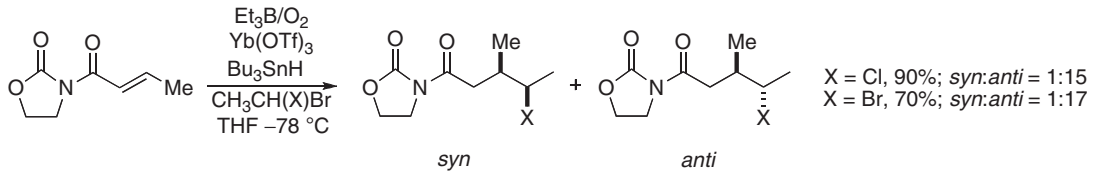
Metzger and coworkers examined the Et_3B initiated and Lewis-acid catalyzed radical conjugate addition to 2-methyl-4-methyleneglutarate (Scheme 28).[56,57] Lewis acid was essential for the reaction, indicating that the reaction takes place under chelation control. The reaction with *t*-Bu radical showed high *syn* selectivity, but increasing the temperature also showed preference for *syn* isomer. Decreasing the size of the radical increased the preference for the *anti* isomer.



R^1	R^2	Temp	Yield	*syn*:*anti*
n-Pr	*t*-Bu	–78 °C	92	98:2
n-Pr	*t*-Bu	70 °C	50	76:24
Me	Et	–78 °C	100	15:85

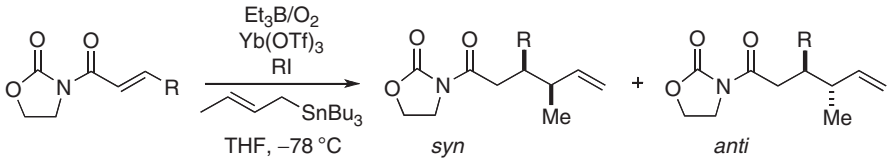
Scheme 28 1,3-Stereoinduction in radical conjugate addition.

Sibi et al. investigated intermolecular diastereoselective radical additions to prochiral acceptors (Scheme 29).[58] In this Lewis-acid ($Yb(OTf)_3$) catalyzed conjugate radical addition, modest *syn* selectivities were obtained for alkyl and α-alkoxy radical additions (6:1). But with less nucleophilic radicals, excellent *anti* selectivity was observed.



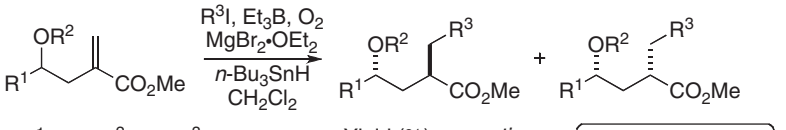
Scheme 29 Diastereoselective prochiral addition to prochiral substrates.

Sibi and coworkers found that the trapping of prochiral α-carbonyl radicals by crotylstannane was catalyzed by Lewis acid ($Yb(OTf)_3$) (Scheme 30).[59] The reaction showed preference for the formation of *syn* product and tertiary alkyl radicals added more effectively and selectively than corresponding secondary and primary alkyl radicals. These results can be explained on the basis of an open transition state where *gauche* interactions are minimized.

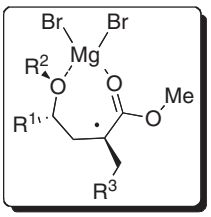


Scheme 30 Lewis-acid catalyzed radical conjugate addition to acrylimide.

Nagano et al. studied isopropyl radical addition to γ-alkoxy-α-methylene esters (Scheme 31). The reaction proceeded with *syn* selectivity in the presence of Mg Lewis acids.[60] Addition of bulky *tert*-butyl radical proceeded with *anti* selectivity, which was explained on the basis of a 7-membered chelated radical intermediate.



R^1	R^2	R^3	Temp (°C)	Yield (%)	*syn:anti*
Ph	Me	*i*-Pr	–78	96	4.3:1
Ph	Me	*t*-Bu	–70	91	1:3.8
Ph	MOM	*i*-Pr	–78	63	2.8:1
t-Bu	MOM	*i*-Pr	–78	78	10:1

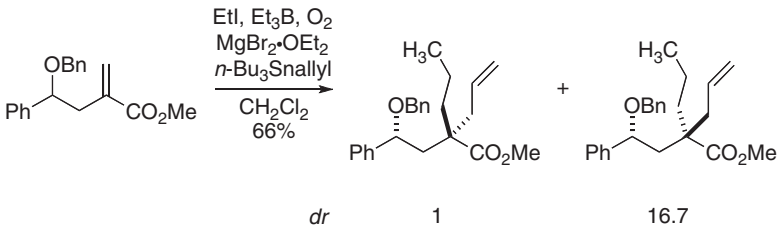


Scheme 31 *Syn*-selective radical conjugate additions.

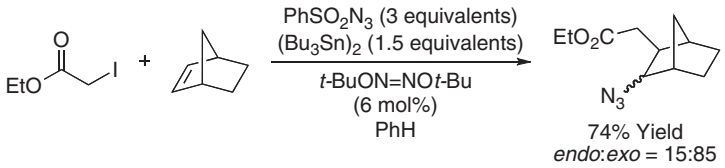
Nagano and coworkers used the same protocol to add isopropyl and *tert*-butyl radical to substrates with a steroidal side chain and obtained high *syn* selectivities for both additions (*i*-Pr addition, 51%, *syn:anti* = 8.8:1; *t*-Bu addition, 68%, *syn:anti* 3.7:1). Nagano and coworkers also examined the possibility of replacing the tin hydride with allyltributylstannane (Scheme 32).[61] Using this protocol, esters, containing α-quaternary centers, could be synthesized efficiently with good control over diastereoselectivity.

Renaud and coworkers have reported intermolecular carboazidation of alkenes (Scheme 33).[62] Ethyl iodoacetate reacted with norbornene to afford the product azide in 74% yield with a selectivity for the *exo* isomer (*endo:exo* = 15:85). Renaud and coworkers have also developed a one-pot procedure for carboazidation of alkenes for the synthesis of various lactams such as pyrrolidinones, pyrrolizidinones and indolizidinones, and spirolactams bearing an amino-substituted quaternary carbon.[63] Recently, the same group has demonstrated the synthetic potential of such processes by reporting the formal total synthesis of lepadiformine.[64] Mechanism of such addition is shown in Scheme 34.

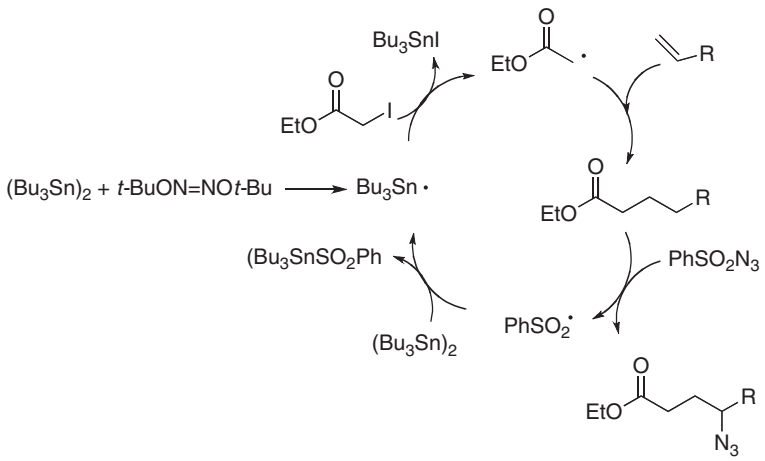
Renaud and Landais studied the diastereoselective carboazidation of chiral allylsilanes, showing that reasonable level of 1,2-diastereocontrol could be achieved starting from readily available β-hydroxysilanes (Scheme 35).[65] A Felkin–Anh-type model was



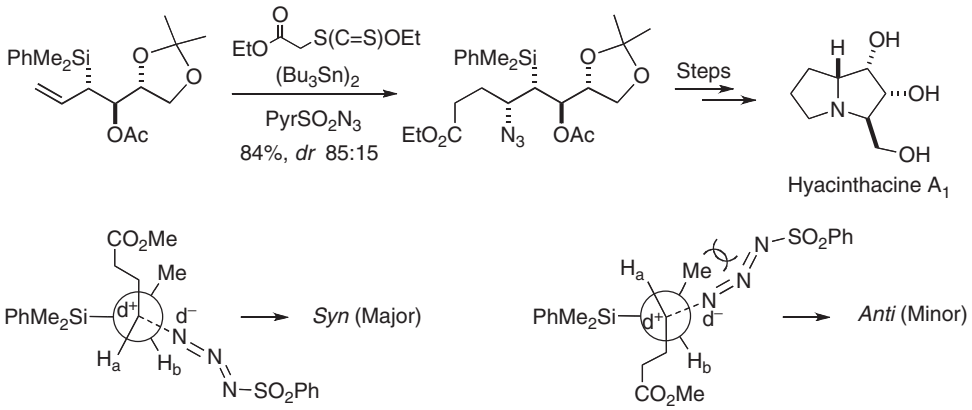
Scheme 32 Formation of quaternary center in conjugate radical addition/trapping.



Scheme 33 Diastereoselective carboazidation of norbornene.



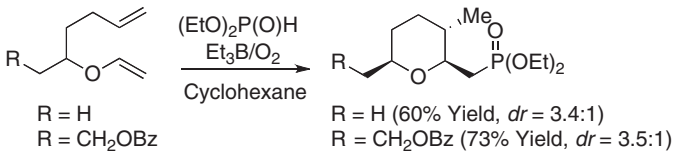
Scheme 34 Mechanism of carboazidation.



Scheme 35 Carboazidation of chiral allylsilanes.

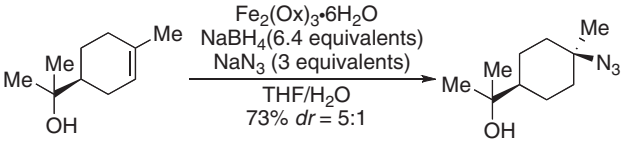
proposed to rationalize the stereochemical outcome of the reaction. Density functional theory (DFT) calculations indicated that the azide approached *anti* relative to the silicon group, for steric reasons, on the side of the smallest substituent (e.g., H). This methodology was then employed as the key step in the first total synthesis of the alkaloid Hyacinthacine A_1.[66]

Heteroatom centered radicals are very important for C–heteroatom bond formation. Such compounds serve as synthetic intermediates in many organic transformations. For instance, Jessop et al.[67] added phosphonyl and thiophosphonyl radicals to enol ethers stereoselectively (Scheme 36). The reaction resulted in the formation of organophosphonates or phosphonothioates. These phosphonate esters are important synthetic intermediates and can be used to prepare stabilized ylides for Wittig reactions.



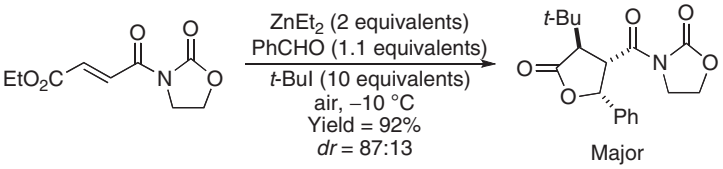
Scheme 36 Diastereoselective addition of phosphonyl radical.

Recently, Boger and coworkers have investigated the hydroazidation of unactivated alkene (Scheme 37).[68] $NaBH_4$ was used as the source of initiating hydride. In the presence of Fe(III) oxalate, styrene, disubstituted, and trisubstituted alkenes, undergo hydroazidation smoothly. Several functional groups were tolerated during the reaction such as unprotected alcohols, amines, epoxides, carboxylic acids, and alkyl bromides. The reaction displayed 5:1 selectivity for the azide delivery. Such reactions are important because azides are not only a precursor for the synthesis of amines but also because of its photoaffinity and its ability to serve as groups for bioconjugates.



Scheme 37 Diastereoselective hydroazidation of unactivated alkenes.

A process that involves the conversion of a radical intermediate to a cation or an anion is called a radical polar crossover reaction. Bertrand and coworkers reported the addition of an alkyl radical to *N*-enoyloxazolidinones followed by trapping with benzaldehyde (Scheme 38).[69,70] The first step is a conjugate addition of *t*-butyl radical to *N*-enoyloxazolidinones resulting in the formation of α-carbonyl radical. This radical reacts with dimethylzinc to form methyl radical and a zinc enolate, which then undergoes controlled aldol reaction with benzaldehyde to form β-hydroxy *N*-enoyloxazolidinones. The imide-alcohol cyclizes to form a lactone.

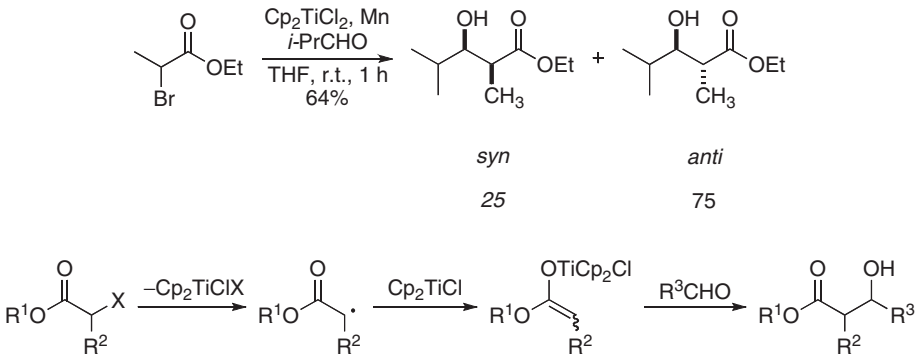


Scheme 38 Radical polar crossover cascade.

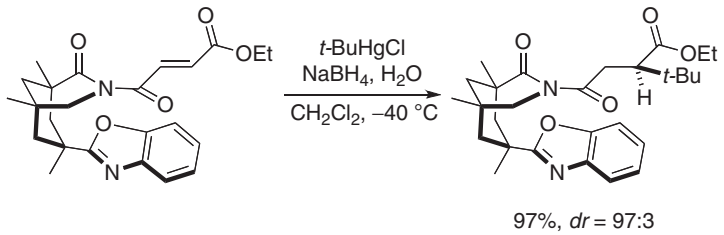
Little et al. reported titanocene(III) promoted Reformatsky-like reactions.[71] The mechanism of the reaction is shown in Scheme 39. The reaction is initiated by one-electron transfer from titanocene(III) to α-bromoketone resulting in the formation of a α-carbonyl radical. Another one-electron transfer process from titanocene(III) results in the formation of a titanium enolate which then adds to aldehydes or ketones to form β-hydroxy esters. The reaction was efficient, giving 78–95% yields for the addition products. When the radical-mediated Reformatsky reaction was carried out with prochiral aldehydes, the addition took place to yield *anti* β-hydroxy esters selectively.

4.12.2.1.1.2 Chiral auxiliary-controlled diastereoselective radical addition

Curran and coworkers used a chiral imide derived from Kemp's triacid as a chiral auxiliary in stereoselective conjugate radical addition of *tert*-butyl radical (Scheme 40).[72,73] The reaction was characterized by high level of diastereoselectivity (*dr* = 97:3). In



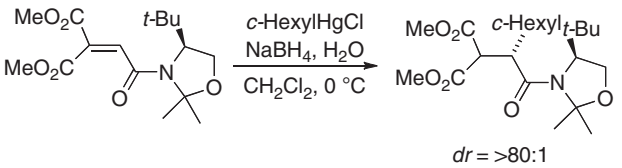
Scheme 39 Titanocene(III)-mediated radical Reformatsky-type reaction.



Scheme 40 Kemp's triacid auxiliary for diastereoselective radical addition.

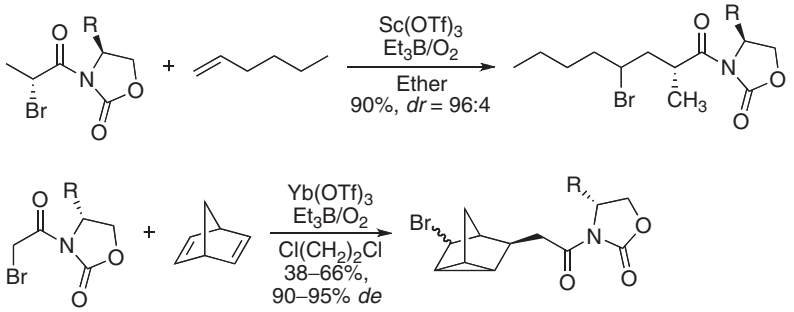
contrast, primary and secondary alkyl radicals added with slightly less selectivity and the auxiliary could be easily cleaved by using LiOOH.

Porter et al. reported the use of *N*-acyl oxazolidines as a chiral auxiliary in intermolecular radical conjugate addition (Scheme 41).[74] The chiral auxiliary can be cleaved by using HCl.



Scheme 41 Chiral oxazolidine auxiliaries for conjugate radical addition.

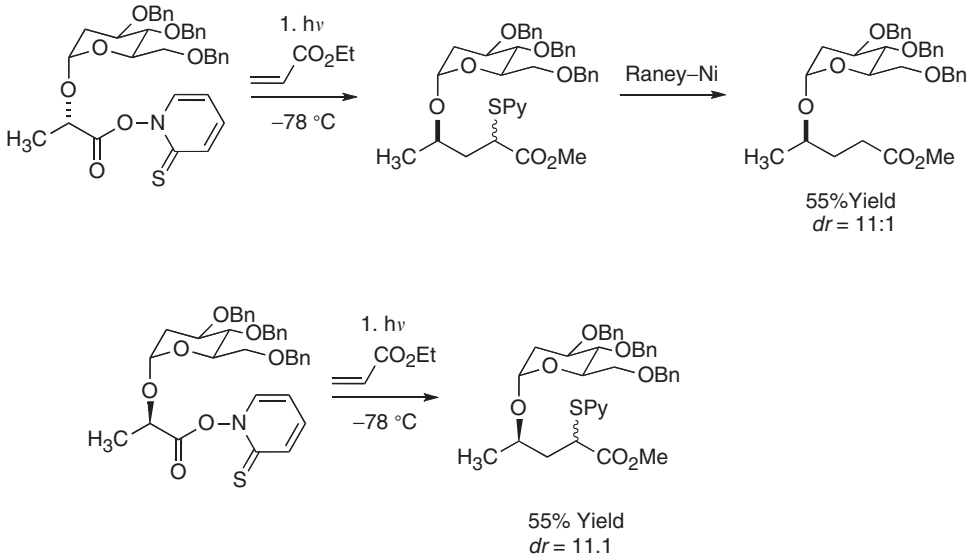
Porter also reported diastereoselective atom-transfer radical additions (Scheme 42).[75] In presence of Lewis acid such as Sc $(OTf)_3$, chiral 2-bromo-acetyl-oxazolidinone adds to 1-hexene efficiently and selectively. The diastereoselectivity of the reaction was measured after radical-mediated reduction of Br followed by removal of the auxiliary. Quantitative yields were obtained for the $Yb(OTf)_3$ catalyzed ATRA to 1-hexene and *cis*-3-hexene. The radical addition to *trans*-3-hexene gave only 63% yield. Recently,



Scheme 42 Stereoselective addition of chiral radicals to alkenes.

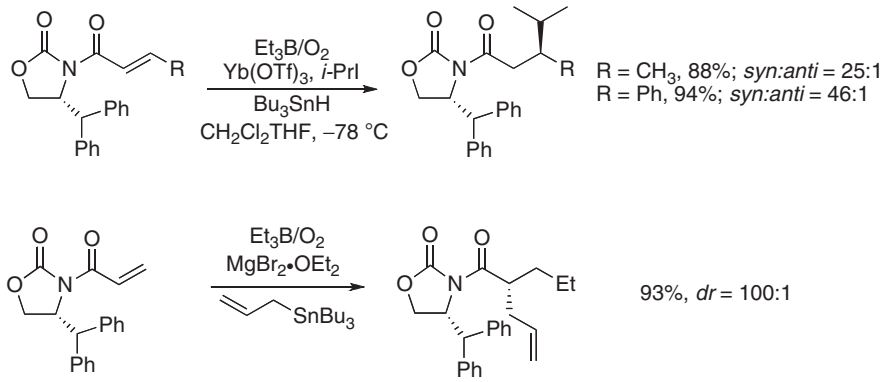
Kavrakova et al. reported similar atom-transfer radical addition to norbornadiene using $Yb(OTf)_3$ as a Lewis acid catalyst (Scheme 42).[76]

Garner et al. used benzylated 2-deoxy-α-glucosyl moiety as a chiral auxiliary in conjugate radical addition reactions.[77] In this report, an effective chiral auxiliary based on 2-tetrahydropyranyl and tri-*O*-benzyl-2-deoxy-R-D-glucopyranosyl for hydroxy radicals have been reported. These chiral radicals were tested for diastereoselective radical additions to acrylates ($dr = 11{:}1$) and nitroolefins (Scheme 43). The auxiliary controls the developing stereochemistry at the radical center. Computational studies showed that the facial selectivity was because of entropic factors in the transition state. The diastereoselectivity of the reaction was calculated after reducing the radical addition products.



Scheme 43 Use of tri-*O*-benzyl-2-deoxy-R-D-glucopyranosyl as chiral auxiliary.

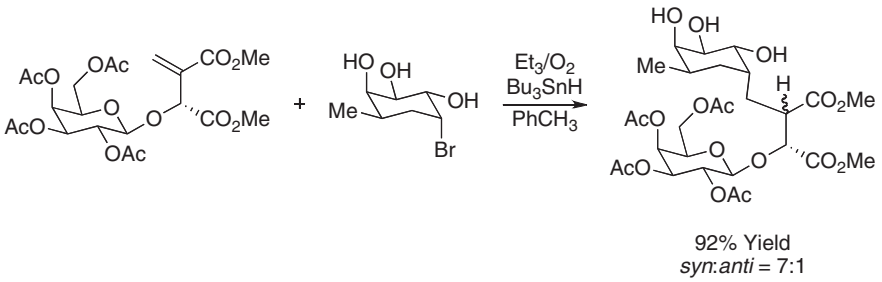
Sibi and coworkers investigated Yb(III)-catalyzed stereoselective radical conjugate addition to *N*-enoyloxazolidinone as shown in Scheme 44.[78,79] The substrate coordinates the Lewis acid and forms a six-membered chelate, which can control rotamer population and hence can achieve highly diastereoselective radical additions. Scheme 44 shows only isopropyl radical addition but other alkyl radicals also add efficiently with diastereoselectivity ranging 25–46:1 for the major isomer. Similar results were obtained for Mg(II) catalyzed radical addition followed by trapping using allylstannanes.



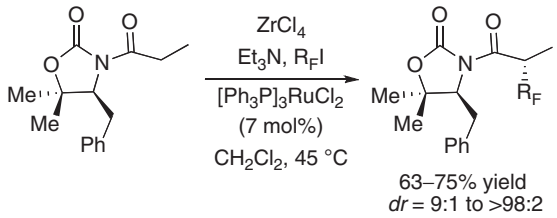
Scheme 44 Stereoselective conjugate radical additions to N-enoyloxazolidinone.

Guindon and coworkers reported the addition of radicals derived from fucosyl bromide.[80] The chiral auxiliary is an α-glucosyl moiety. The reaction showed very high selectivity for the formation of the *syn* isomer (Scheme 45).

Recently, Zakarian and coworkers reported the diastereoselective trifluoromethylation of *N*-acyloxazolidinones using ruthenium catalyzed radical addition to zirconium enolates (Scheme 46).[81] Several perfluoroalkyl radicals generated from the corresponding iodides underwent reactions with high chemical efficiency and high stereoselectivity (>98:2 in most cases). This study has also shown functional group compatibility with aromatic and heteroaromatic substituents.



Scheme 45 Selective α-C-glycosylation followed by H-atom transfer.

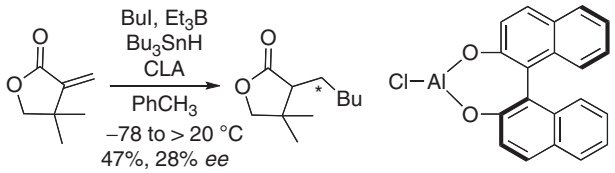


Scheme 46 Perfluoroalkylation of N-acyloxazolidinones using Ru-catalysis.

4.12.2.1.2 Enantioselective radical additions to carbon–carbon multiple bonds

Chiral Lewis acids (CLAs) are indispensable reagents for synthetic chemists when it comes to the synthesis of enantiopure compounds. Several asymmetric organic transformations have been achieved by employing these reagents. The CLA can bind to the substrate (radical acceptor) or the radical species or both, thereby increasing the reactivity as well as the selectivity of the radical process.

Sato et al. reported the first enantioselective conjugate addition of radicals.[55] In this report they studied the asymmetric H-atom-transfer process to a carbon radical generated by conjugate addition of butyl radical to α-methylenebutyrolactone in the presence of a strong chiral aluminum Lewis acid. An aluminum Lewis acid effected modest asymmetric transfer (28% *ee*) of hydrogen atom to the radical generated α to the carbonyl group (Scheme 47). A single point coordination of the substrate to the chiral aluminum Lewis acid would explain the stereoselectivity of H-atom transfer.

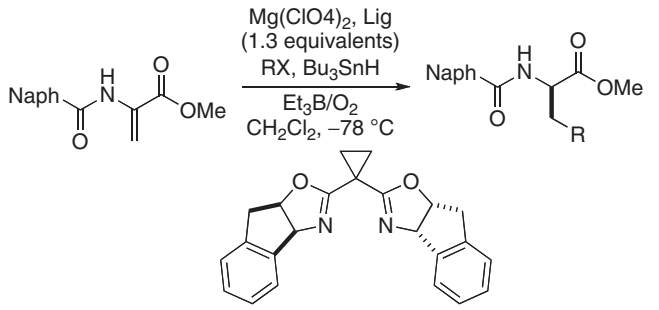


Scheme 47 Chiral aluminum Lewis-acid catalyzed asymmetric H-transfer.

Sibi and coworkers studied enantioselective hydrogen atom transfers to substrates capable of making bidentate coordination to the Lewis acid.[82] Several nucleophilic radicals (alkyl and α-alkoxy) were added to the dehydroalanine-like substrates in the presence of $Mg(ClO_4)_2$ and a bisoxazoline ligand to furnish the adducts in good yields and enantioselectivities. Although primary and secondary alkyl radicals added with good selectivities (55–85% *ee*), *t*-butyl radical addition gave very poor selectivity (27% *ee*, Scheme 48). The decrease in selectivity was attributed to the *tert*-butyl group shielding the opposite face to the CLA resulting in the reaction occurring from a mono-coordinated substrate. Even though the enantioselectivities were modest, more than one equivalent of CLA was used in the reaction.

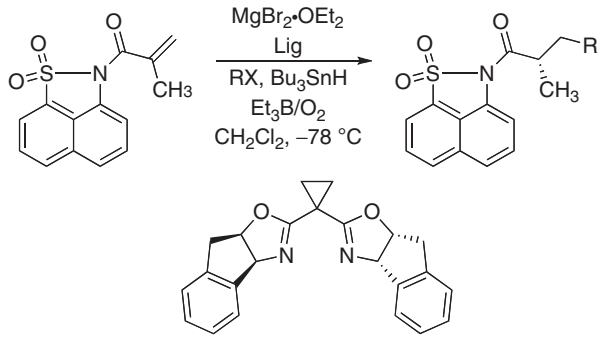
Sibi et al. also reported enantioselective H-atom transfer to substrates derived from commercially available 1,8-naphthosultam which can coordinate to the Lewis acid in a bidentate fashion.[83] Unlike the previous example, this procedure works well with tertiary radical (Scheme 49) and the main advantage of this method is that even catalytic amounts of CLA (30 mol%) is sufficient to effect good enantioselectivity.

Sibi and Porter reported the first enantioselective conjugate addition of nucleophilic radicals to more electrophilic double bonds in a conjugated system.[84,85] The conjugate addition of isopropyl radical to a bidentate coordinating substrate derived from oxazolidinone in the presence of substoichiometric amounts of MgI_2 and bisoxazoline ligand proceeded with high chemical efficiency and high enantioselectivity (88% yield; 95% *ee*; Scheme 50). It was proposed that the chelation of the substrate to the



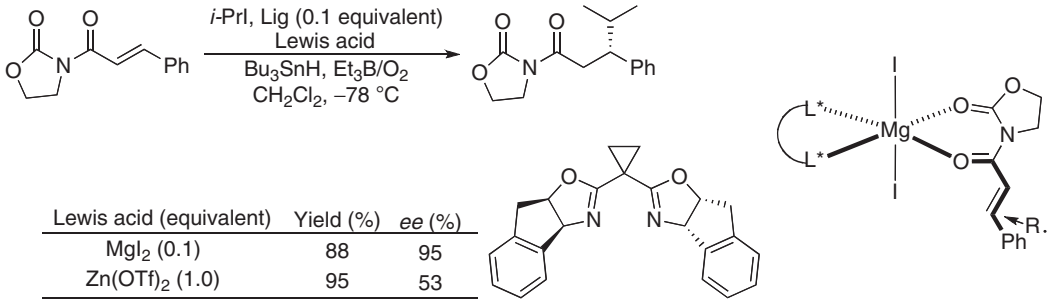
RX	Yield (%)	*ee* (%)
AcBr	76	80
$MeOCH_2Br$	71	65
EtI	72	85 (R)
i-BuI	76	79
i-PrI	62	83 (R)
c-HexI	62	55 (R)
t-BuI	54	27 (R)

Scheme 48 Chiral Lewis acid-mediated enantioselective H-atom transfer.



RX	equivalent of Lewis acid	Yield (%)	*ee* (%)
i-Pr	1.0	90	78
i-Pr	0.3	55	80
c-Hex	0.3	84	89
t-Bul	0.3	71	82
$MeOCH_2$	0.3	89	90

Scheme 49 Enantioselective H-atom transfer to naphthosultams.



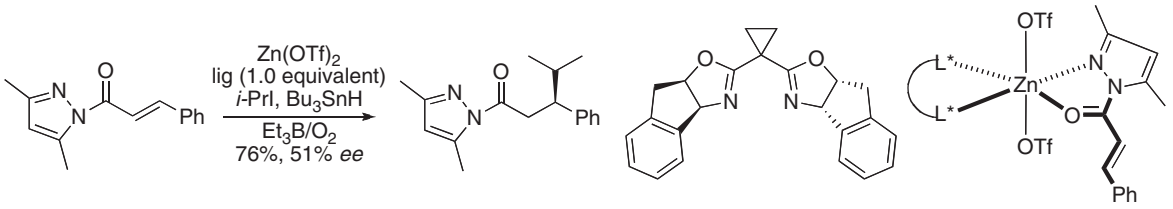
Lewis acid (equivalent)	Yield (%)	*ee* (%)
MgI_2 (0.1)	88	95
$Zn(OTf)_2$ (1.0)	95	53

Scheme 50 Enantioselective radical addition to conjugated systems using chiral Lewis acids.

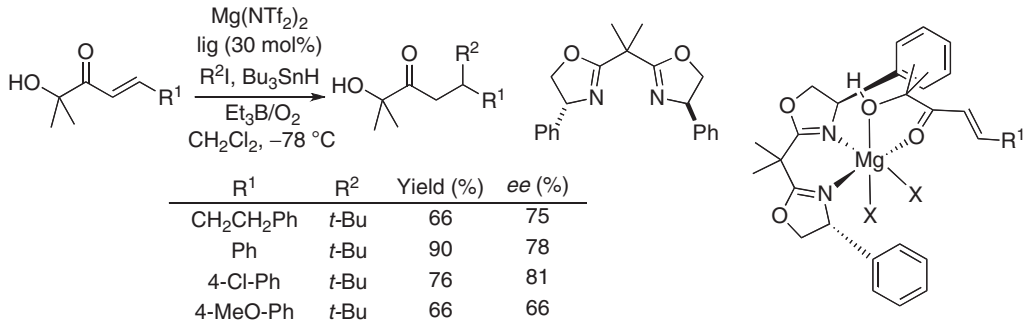
CLA enables the substrate in achieving s-*cis* conformation at C(O)–C(sp^2) bond to provide optimal facial selectivity for the radical. A stereochemical model proposed for the reaction in also shown in Scheme 50.

Sibi et al. have evaluated the role of the achiral template in the outcome of the stereoselectivity of radical addition.[86] Changing the oxazolidinone template to a pyrazole template resulted in the reversal of enantioselectivity. Alkyl radical addition in the presence of stoichiometric amounts of $Zn(OTf)_2$ and bisoxazoline ligand resulted in the formation of adduct in high chemical yield and moderate enantioselectivity (51% *ee*). The substrate forms a five-membered chelate as opposed to six-membered chelate in the case of acyl oxazolidinone. The differences in chelate ring size along with *trans*-octahedral geometry of the chelate were proposed to be the reasons for the reversal of selectivity (Scheme 51).

Sibi and Kim used α-hydroxyenones as bidentate substrates in enantioselective intermolecular radical addition reactions.[87] In the presence of catalytic amount of $Mg(NTf_2)_2$ and box ligand, nucleophilic radicals add to hydroxyenones efficiently in a conjugate fashion (Scheme 52). This procedure showed very good substrate as well as radical scope. The *ee*'s for the adducts ranged from 66% to 86%. The addition of *tert*-butyl radical to electron-deficient 4-chlorophenyl substituted enone is more selective (81% *ee*) than the addition to electron-rich 4-methoxyphenyl substituted enone (66% *ee*). Although the enantiopurity is not very high, this synthetic procedure can work for various alkyl radicals. The absolute stereochemistry of the product was found to be *R*. A simple model that explains the observed facial selectivity is shown in Scheme 52. The substrate forms a *cis*-octahedral complex in which the N-atoms of the box ligands occupy the equatorial position, the carbonyl group of the substrate occupying



Scheme 51 Effect of template on the outcome of enantioselectivity in asymmetric radical additions.

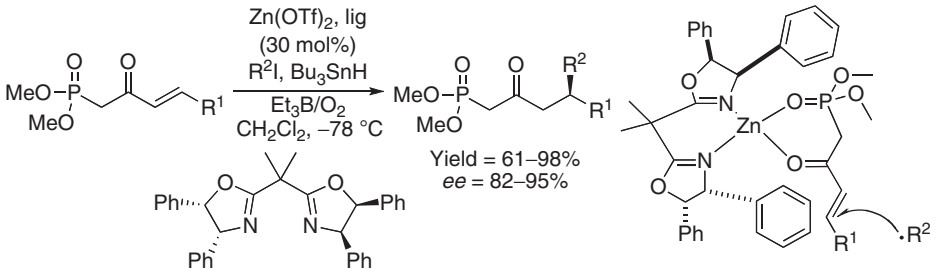


R^1	R^2	Yield (%)	*ee* (%)
CH_2CH_2Ph	*t*-Bu	66	75
Ph	*t*-Bu	90	78
4-Cl-Ph	*t*-Bu	76	81
4-MeO-Ph	*t*-Bu	66	66

Scheme 52 Enantioselective radical additions to α-hydroxyenones.

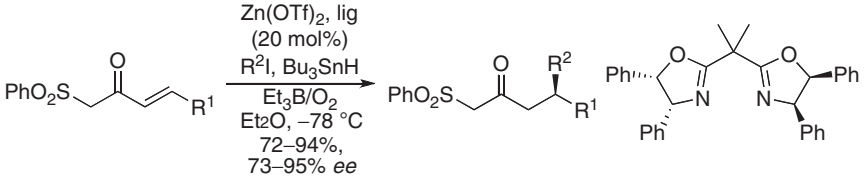
an equatorial position and the hydroxyl occupying an axial position. In this particular organization, the phenyl group on the box ligand offers effective shielding of one face of the double bond resulting in good enantioselectivity.

Kim and coworkers reported enantioselective radical additions to α-ketophosphonates (Scheme 53).[88] Among the several CLAs screened, catalytic amounts of $Zn(OTf)_2$ and box ligand gave excellent enantioselectivities for the nucleophilic radical addition to C=C double bonds (Scheme 53). The reaction condition was tolerant to different substituents in the *β*-position. Several nucleophilic radicals added smoothly with high yield (61–98%) and good enantioselectivities (82–95% *ee*). The absolute stereochemistry for the product was found to be S and a working model with Zn in tetrahedral coordination geometry has been postulated.



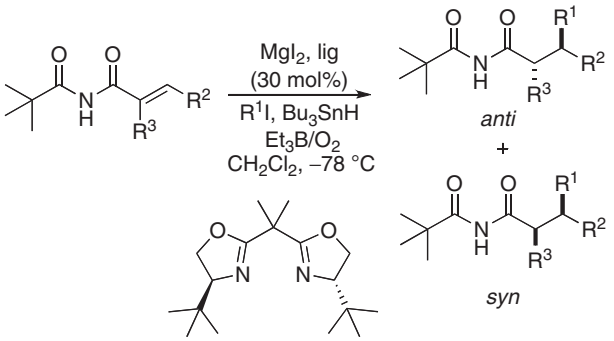
Scheme 53 Asymmetric radical additions to α-ketophosphonates.

Recently, Kim and coworkers reported the asymmetric addition of nucleophilic radicals to α′-phenylsulfonylenones in the presence of $Zn(OTf)_2$ and box ligand (Scheme 54).[89] The reaction showed a strong dependence on solvent and ether was found to be the best solvent for this system. The radicals added efficiently, with very high chemical yields (72–94%) and good enantioselectivities (73–95% *ee*). A tetrahedral model with *Si*-face attack of the radical was invoked to explain the observed selectivity.



Scheme 54 Enantioselective radical additions to α′-phenylsulfonylenones.

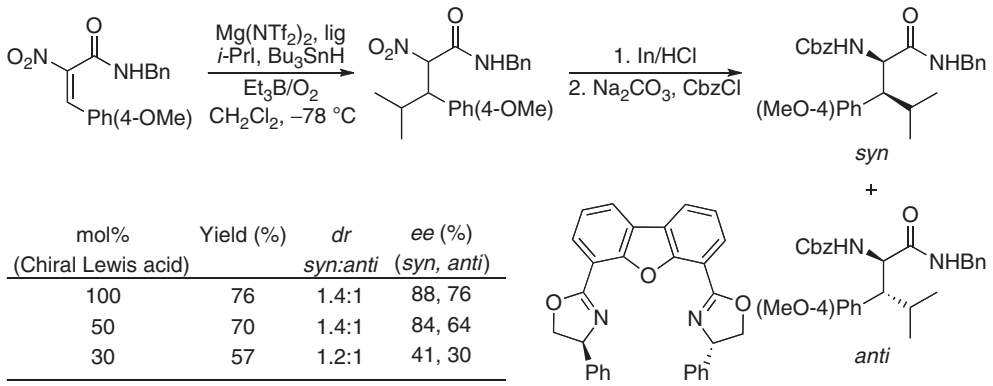
Sibi and coworkers reported asymmetric radical addition to electron-deficient α,β-disubstituted C=C bonds.[90] These substrates are very unreactive because of both electronic and steric reasons. In this report, *tert*-butyl imide was used as the template. This template increased the reactivity of the substrates and also controlled the rotamer populations in substituted acrylates. MgI_2 and box ligands were used as CLAs in this reaction. Radicals add smoothly to tiglates in the presence of CLAs to afford adducts in good yield and very high stereoselectivities (both diastereo- and enantioselectivities, Scheme 55). In all the cases, *anti* diastereomer was obtained as the major product (*dr* = 87:13 to 99:1). The *ee*'s for the *anti* product ranged from 74% to 94%.



R^1	R^2	R^3	Yield (%)	*anti:syn*	*ee* (%)
Et	Me	Me	63	87:13	92
i-Pr	Me	Me	79	99:1	92
t-Bu	Me	Me	83	99:1	94
i-Pr	Et	Me	37	95:5	80
i-Pr	Ph	Me	71	99:1	93
i-Pr	Me	Et	50	87:13	74

Scheme 55 Asymmetric radical additions to tiglates.

Castle et al. have examined the enantioselective radical additions to β-substituted-α,β-unsaturated-α-nitro esters and amides (Scheme 56).[91,92] Stoichiometric amounts of $Mg(NTf_2)_2$ and DBFOX/Ph derived CLAs effected the addition of alkyl radicals to α,β-unsaturated-α-nitro amides. For these additions, the diastereomeric ratio was close to 1:1 with a slight preference for the *syn* isomer. The enantioselectivity of the reaction was found to be highly dependent on the amount of CLA used. Erosion of enantiopurity was seen with a decrease in the amount of Lewis acid. Studies on the origin of stereoselectivity also revealed that the H-atom-transfer step is more selective than the radical addition step.



mol% (Chiral Lewis acid)	Yield (%)	*dr* *syn:anti*	*ee* (%) (*syn*, *anti*)
100	76	1.4:1	88, 76
50	70	1.4:1	84, 64
30	57	1.2:1	41, 30

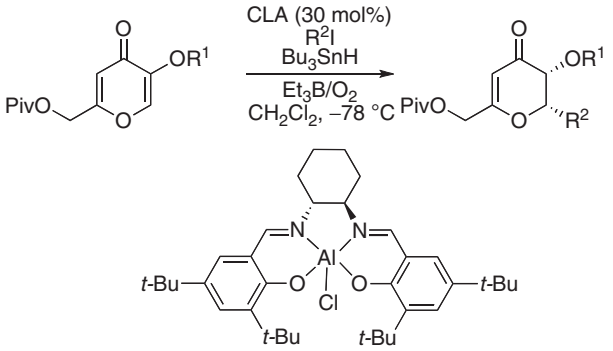
Scheme 56 Radical additions to β-substituted-α,β-unsaturated-α-nitro amides.

Sibi et al. have studied radical additions to hydroxypyrones using CLAs.[93] Commercially available kojic acid derivatives were used as the substrates. Since the substrate has a built in s-*trans* geometry of the double bond, there was no need for an external template. In the presence of substoichiometric amounts of chiral aluminum salen Lewis acids (salen = *N*, *N*′-bis(salicylidene) ethylenediamine anion), radicals add with high chemical efficiency and good enantioselectivity (Scheme 57). For all the cases excellent *dr*'s and *ee*'s were obtained.

Sibi and coworkers have reported conjugate radical additions to exomethylene cyclohexanones with an s-*cis* geometry.[94] Chiral salen derived aluminum Lewis acids were found to catalyze isopropyl radical additions to afford adducts with very high selectivity (*dr* = 99:1; 95% *ee*). This method provides a way to synthesize cyclic aldols by radical addition with the formation of two contiguous stereocenters with high selectivity (Scheme 58).

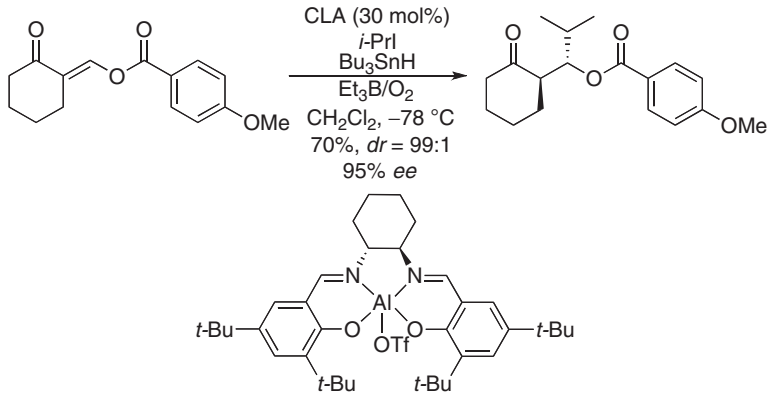
Porter et al. reported the first asymmetric radical addition/fragmentation reactions.[95] Using stoichiometric amount of Zn $(OTf)_2$ and box ligand, alkyl radicals were added to oxazolidinone-derived acrylates (Scheme 59). The resultant α-acyl radicals were trapped with allyltributylstannane to afford adducts in good yield and high enantioselectivity. The reaction is highly dependent on the solvent system and CH_2Cl_2/pentane was found to be optimal.

Sibi et al. reported radical addition/fragmentation reactions of oxazolidinone-derived β-substituted acrylates.[96] The radicals add to β-substituted acrylates in the presence of CLA followed by allylation, which gave adducts with two contiguous stereocenters

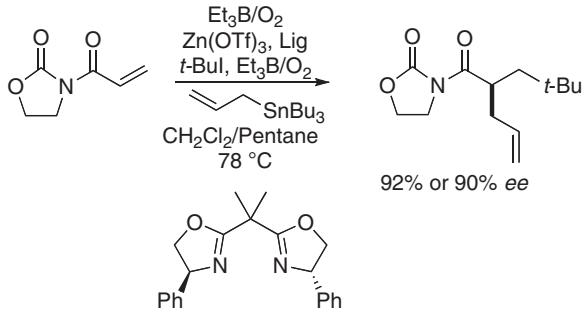


R^1	R^2	Yield (%)	*dr*	*ee* (%)
H	*i*-Pr	85	99:1	74
H	*c*-Pentyl	67	99:1	76
H	*t*-Bu	91	99:1	92
H	$(CH_3)_2C(CH_2)_3Cl$	35	99:1	92
Piv	*i*-Pr	92	99:1	72
Piv	*c*-Pentyl	74	99:1	76
Piv	*t*-Bu	96	99:1	93
Piv	$(CH_3)_2C(CH_2)_3Cl$	77	99:1	90

Scheme 57 Chiral aluminum Lewis-acid catalyzed conjugate addition to pyrones.



Scheme 58 Synthesis of cyclic aldol-type products by asymmetric radical conjugate addition.



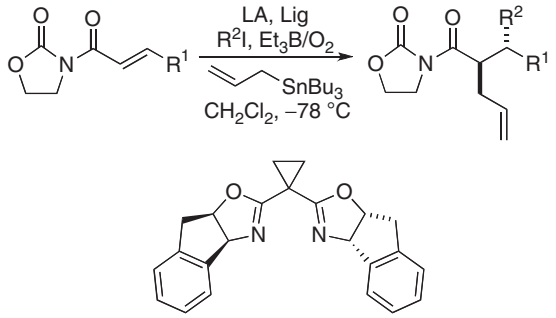
Scheme 59 Asymmetric radical addition-fragmentation reaction.

with excellent diastereoselectivity and enantioselectivity (Scheme 60). By changing the Lewis acid to Cu(II) from Mg(II), reversal of enantioselectivity was obtained.

Recently, Kim reported radical addition/fragmentation using α-ketophosphonates (Scheme 61).[89] The intermediate radical formed after the initial radical addition was trapped with allyltributylstannane to yield adducts in high diastereoselectivity (>50:1, *anti* diastereomer) and enantioselectivity (99% *ee*).

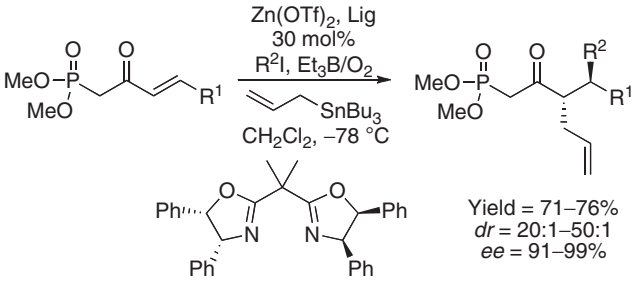
4.12.2.1.2.1 Organocatalysis

The field of organocatalysis[97] has seen an enormous growth.[98,99] In addition to traditional modes of activation by aminocatalysis (imine, enamine, and dienamine activation), a new mode of catalytic activation based on single-electron transfer (SET) oxidation has been proposed by MacMillan.[100] In this new mode of activation, a transient enamine undergoes SET to form a radical cation intermediate that reacts with radical traps to form functionalized compounds. The generally accepted mechanism for SOMO catalysis is shown in Scheme 62.

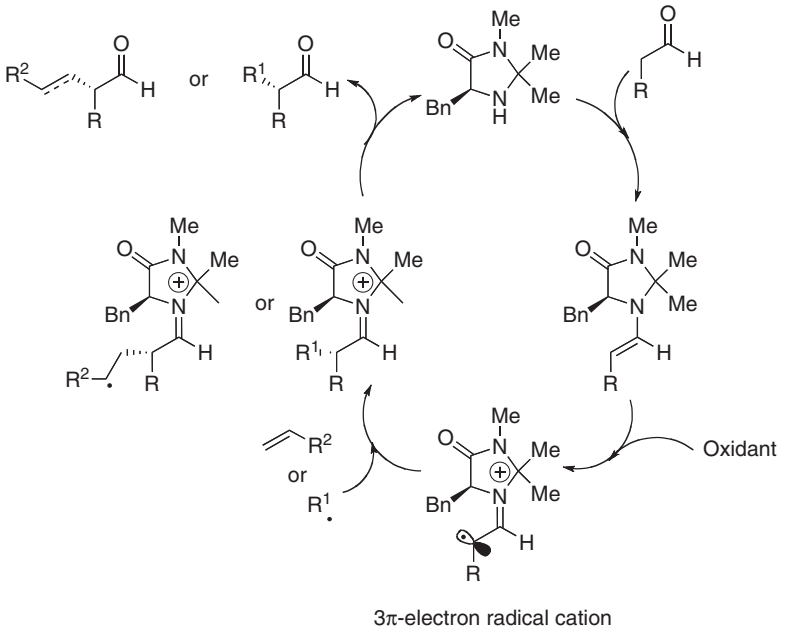


R^1	R^2	LA	Yield (%)	*dr*	*ee* (%)
Ph	Et	MgI_2	79	32:1	77
Ph	*i*-Pr	MgI_2	93	37:1	93
Ph	*t*-Bu	MgI_2	84	99:1	97
Ph	*t*-Bu	$Cu(OTf)_2$	90	99:1	–96
CH_3	*c*-Hexyl	$Mg(ClO_4)_2$	83	4:1	62

Scheme 60 Asymmetric radical addition/fragmentation to construct two stereocenters.

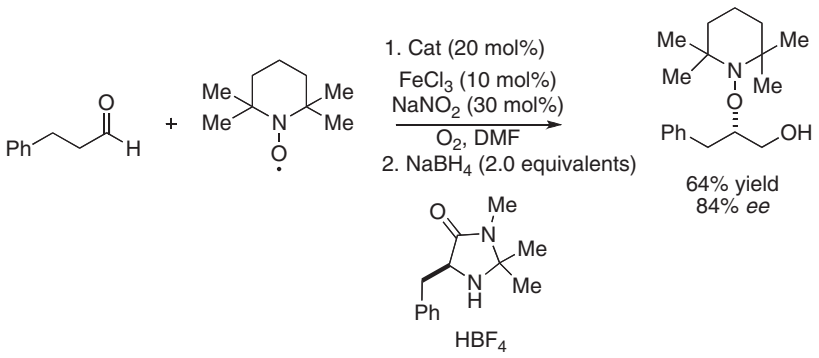


Scheme 61 Enantioselective addition/fragmentation of α-ketophosphonates.



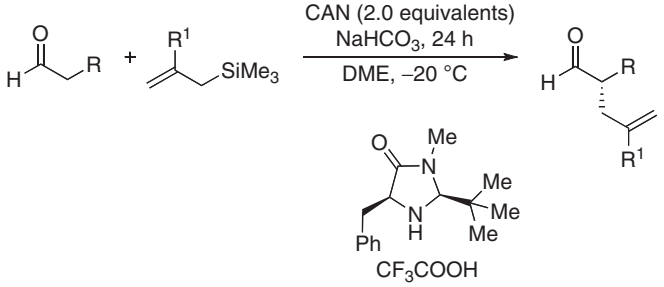
Scheme 62 Mechanism of SOMO catalysis.

Sibi et al. used such activation for the enantioselective α-oxyamination of aldehydes (Scheme 63).[101] The reaction involves SOMO activation of the enamine formed from the initial condensation of the aldehyde and imidazolidinone catalyst and 2,2,6,6-tetramethylpiperidin-1-y1oxyl (TEMPO) as the oxygen trap. In this reaction, substoichiometric amounts of $FeCl_3$ and $NaNO_2/O_2$ were used as the SET reagent. Several aldehydes were oxidized to α-radical cation intermediates, which were then trapped by TEMPO to form α-oxyaminated aldehydes. The reaction was shown to be solvent and temperature dependent. Moderate to good enantioselectivities were obtained for the process.



Scheme 63 Organocatalyzed asymmetric α-oxyamination of aldehydes.

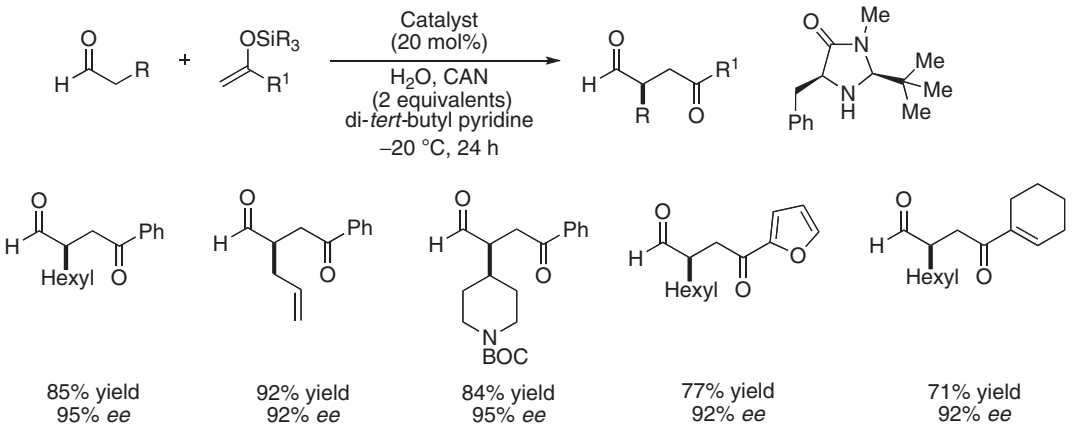
MacMillan et al. employed SOMO-activated enamines in allylic alkylation of aldehydes (Scheme 64).[100] The cationic radical intermediate obtained by the oxidation of the enamine was subjected to reaction with electron-rich allylsilanes, followed by oxidation and removal of silyl group led to the formation of γ,δ-unsaturated aldehydes. This is an example of double oxidative C–C bond formation. The reactions are highly efficient in terms of yield and enantioselectivities (87–95% *ee*). The reaction is tolerant to much chemical functionality such as esters, olefins, and ketones. The reaction efficiency and enantioselectivities are unchanged with the size of R group.



R	R^1	Yield (%)	*ee* (%)
$(CH_2)_4CH_3$	H	81	91
$(CH_2)_7CH{=}CH_2$	H	75	92
$(CH_2)_7CH_2OBz$	H	72	95
$(CH_2)_3CO_2Me$	H	72	87
c-Hexyl	H	75	94
$(CH_2)_4CH_3$	Me	88	91
$(CH_2)_4CH_3$	Ph	87	90
$(CH_2)_4CH_3$	CH_2Bn	77	88
$(CH_2)_4CH_3$	CO_2Et	81	90

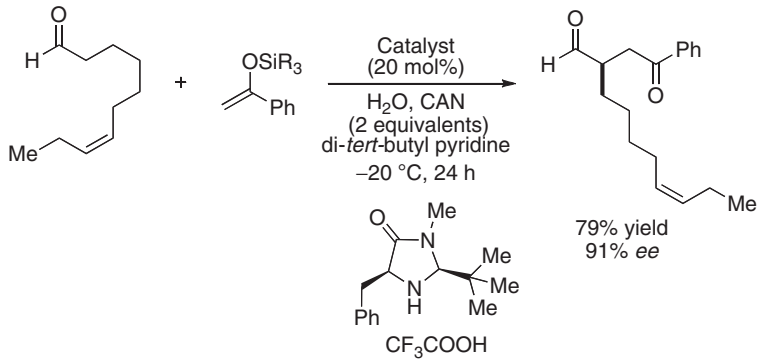
Scheme 64 Enantioselective α-allylation of aldehydes.

Using organocatalytic SOMO activation, MacMillan et al. developed a novel method for the α-enolation of aldehydes (Scheme 65).[102] By using this protocol, enantioenriched γ-ketoaldehydes can be synthesized starting from simple aldehydes. The chemical efficiency is dependent up on the amount of oxidant and H_2O and also the use of 2,6-di-*tert*-butyl pyridine as the base. Functionalities such as olefins remain inert under the reaction conditions. As can be seen from Scheme 65, not only simple aldehydes, but ones with other functionalities such as olefins, aryl rings, and carbamates can also undergo this kind of reaction with ease. A wide variety of π-electron-rich enolsilanes can be used as somophiles in the reaction. Enolsilanes with aryl, alkyl, and vinyl groups are tolerated in the reaction (Scheme 65).



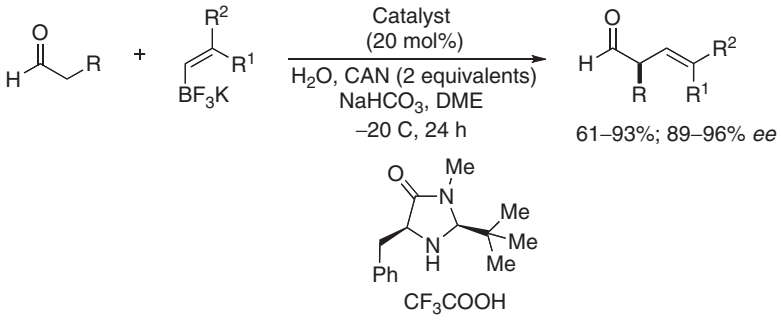
Scheme 65 Enantioselective α-enolation of aldehydes.

MacMillan and coworkers were able to showcase the ability of putative radical cation to undergo intermolecular enolation than intramolecular cyclohexyl ring formation with π-electron-rich olefins (Scheme 66).[102]



Scheme 66 Intermolecular enolation versus intramolecular cyclization.

Despite the advances in transition metal catalyzed enolate-aryl coupling reactions, enantioselective enolate-vinyl coupling reactions are less known in the literature.[103,104] This is mainly because the stereocenter is destroyed via epimerization and subsequent isomerization of the double bonds to α,β-unsaturated carbonyl products. Recently, MacMillan and coworkers have reported asymmetric α-vinylation of simple aldehydes using organo-SOMO catalysis.[105] α-Vinylation is achieved by using vinyltrifluoroborate salt and imidazolidinone catalyst (Scheme 67). The importance of this mild protocol lies in the fact that it enables synthetic chemist to synthesize methine stereogenic centers without any disposition of olefinic bonds and loss in enantioselectivity. These reactions showed high enantioselectivity with the preference for *trans* olefin geometry. The reaction conditions are highly functional group tolerant and the efficiency of the enantioselective process does not depend on the steric demands of the aldehyde.

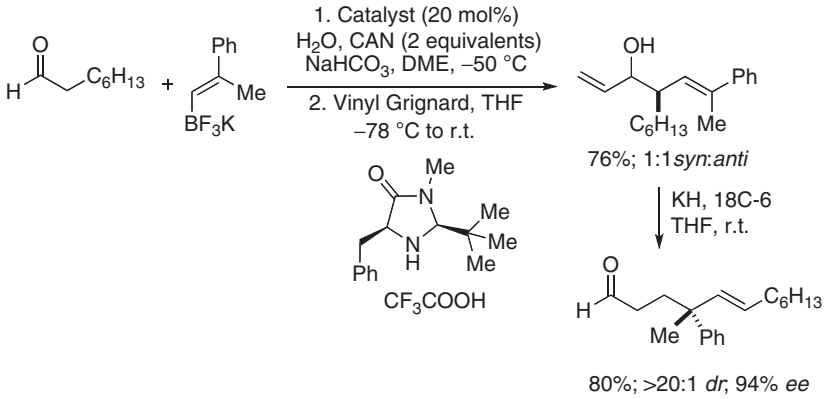


Scheme 67 SOMO-catalyzed enantioselective vinylation of aldehydes.

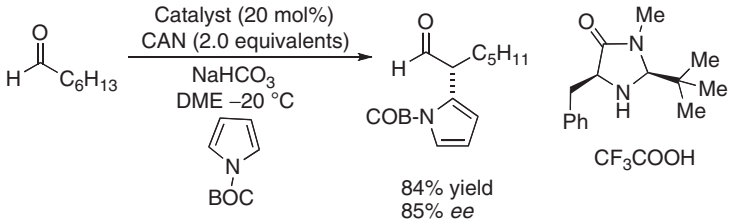
MacMillan and coworkers also demonstrated the synthetic utility for adducts formed from vinylation of aldehydes (Scheme 68). When octanal was subjected to asymmetric vinylation followed by *in situ* vinyl Grignard addition, 1,5-dienyl alcohol was obtained in 76% yield with no diastereocontrol. When this alcohol was subjected to anionic oxy-Cope protocol, an aldehyde bearing quaternary carbon was formed as a single diastereomer with complete retention of stereochemistry. This strategy might be applicable in synthesis as an alternative to oxy-Cope retron.

MacMillan and coworkers reported the asymmetric α-arylation of aldehydes. An intermolecular reaction between heptanal and pyrrole was mediated by an imidazolidinone catalyst (Scheme 69). The arylated product was obtained in 84% yield and 85% *ee*.

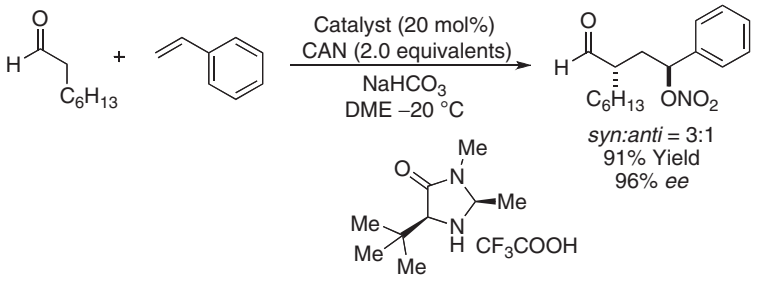
MacMillan and coworkers have also examined the possibility of using styrenes as somophiles.[106] The cation radical generated from the catalyst and aldehyde on exposure to styrene formed γ-nitrate aldehydes in good yields, modest diastereoselectivity, and high enantioselectivity (Scheme 70). Initial addition of cationic radical to styrene results in the formation of a C-centered radical at γ position to the aldehyde, which on SET forms a cation. The cation on reaction with nitrate ion forms γ-nitrate aldehydes. β-substituted styrenes were also competent somophiles in the reaction giving a product with three stereogenic centers.



Scheme 68 Synthetic utility of asymmetric α-vinylation of aldehydes.



Scheme 69 Asymmetric organocatalyzed α-arylation of aldehydes.



Scheme 70 Enantioselective carbo-oxidation of styrenes.

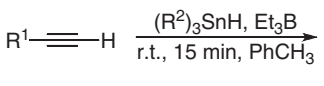
4.12.2.2 Free-Radical Addition to Carbon–Carbon Triple Bonds

4.12.2.2.1 Radical additions to alkynes

Oshima et al. were the first to report triethylborane-mediated hydrostannylation of alkynes (Scheme 71).[107] Et_3B was found to be superior to AIBN and benzoylperoxide. This initiator can generate radicals at low temperature with high selectivity. In this report Oshima and coworkers found that using catalytic amount of Et_3B, hydrostannylation of several terminal alkynes could be achieved with good chemical efficiency and a preference for the formation of the E-isomer of the hydrostannylated product (Scheme 71).

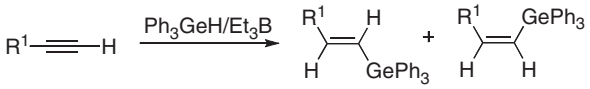
Oshima et al. also found that germanes could be added across alkynes stereoselectively in the presence of a catalytic amount of triethylborane (Scheme 72).[108] Both E and Z isomers could be obtained by altering the reaction conditions: at $-78\,^{\circ}C$, the reaction showed preference for the E-isomer and at $60\,^{\circ}C$, the reaction showed preference for the Z-isomer. Similarly, Et_3B-mediated stereoselective addition of tris(trimethylsilyl)silane (TTMSS) and benzenethiol to alkynes were also reported by Oshima et al.[109,110]

Recently, Guo and coworkers have examined dimethylzinc-mediated radical addition of ethers to alkynes. 2-Vinylether derivatives were obtained as products with high E-selectivity. The selectivity could be reversed by changing to triethylborane/O_2 system as the initiator (Scheme 73).[111] Two competing pathways explaining the selectivity was proposed: (1) zinc radical exchange and



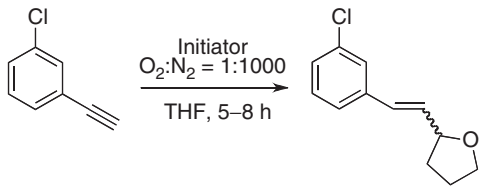
R^1	R^2	Yield (%)	**E:Z**
n-$C_{10}H_{21}$	Ph	80	79:21
n-$C_{10}H_{21}$	n-Bu	40	80:20
$HOCH_2CH_2$	Ph	87	82:18
Ph	Ph	75	100:0
Me_3Si	Ph	83	100:0

Scheme 71 Et_3B initiated hydrostannylation of alkynes.



R^1	Temp (°C)	Yield (%)	**E:Z**
n-$C_{10}H_{21}$	–78	76	>20:1
n-$C_{10}H_{21}$	60	99	1:20
$HOCH_2CH_2$	–78	80	>20:1
$HOCH_2CH_2$	60	75	1:20
$EtOOC(CH_2)_9$	–78	64	>10:1
$EtOOC(CH_2)_9$	60	93	1:20

Scheme 72 Et_3B-mediated addition of triphenylgermanes across alkynes.

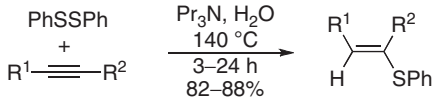


Initiator (equivalent)	Yield (%)	**E:Z**
Me_2Zn (3)	24	13.5:1
Et_2Zn(3)	18	5.6:1
Me_2Zn(8)	53	20:1
Et_3B(3)	33	1:2.3
Et_3B(5)	60	1:2.3

Scheme 73 Radical addition of ethers to alkynes.

protonation of the resulting Zn(II) complex to furnish the E-alkene. (2) Radical addition followed by hydrogen atom abstraction by the vinyl radical provides the Z-alkene.

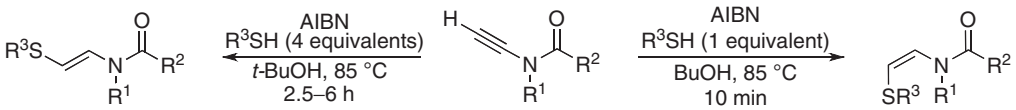
Ishibashi and coworkers reported the hydrothiolation of alkynes using diphenyl disulfide in the presence of amines (Scheme 74).[112] Among the amines surveyed, it was found that the use of propylamine increased the chemical yield and selectivity (E:Z=85:15). With terminal alkynes, modest to good selectivities were obtained but with internal alkynes the selectivities were low. The proposed mechanism involves SET from amine to diphenyl disulfide.



E:Z = 1.32:1 – 5.67:1

Scheme 74 Hydrothiolation of alkynes.

Recently, Castle and coworkers reported the addition of thiyl radicals to ynamides.[113] AIBN mediated addition of thiols to ynamides under different sets of conditions proceeded with good yield and high selectivity. With 4 equivalents of thiol, there was a high preference for the E-isomer. But when 1 equivalent of thiol was used, Z-isomer was the major product (Scheme 75).



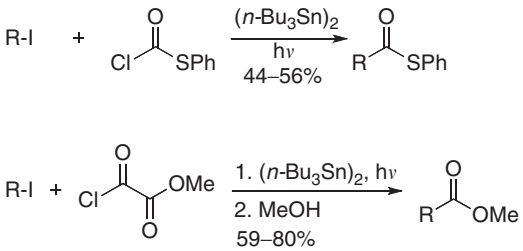
Scheme 75 Addition of thiyl radicals to ynamides.

4.12.3 Free-Radical Addition to Carbon–Heteroatom Multiple Bonds

4.12.3.1 Free-Radical Additions to Carbon–Oxygen Double Bonds

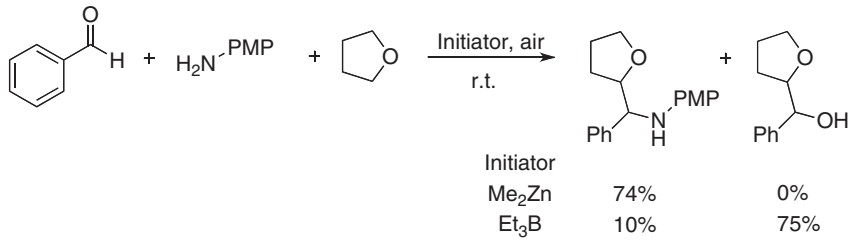
Owing to the strong carbon–oxygen π-bond strength, the addition of radicals to carbonyl groups is thermodynamically an unfavorable process and is often reversible. Also the resultant oxy radicals formed from such an addition process are highly unstable and often undergo fragmentation. The process of oxy radical fragmentation is faster than addition itself. The carbonyl groups are not efficient radical traps when compared to alkenes and alkynes and hence such additions are rarely reported in the literature.

Early reports on using carbonyl groups as radical traps appeared in 1942.[114,115] Kharasch and Brown examined the radical-mediated carboxylation of saturated and unsaturated hydrocarbons using oxalyl chloride as the radical trap. Biacetyl was used as a radical trap in the acetylation of alkyl radicals.[116] On a similar note, Kim and coworkers have used other acid derivatives as radical traps for both intermolecular[117,118] and intramolecular[119] alkyl radical additions. In the intermolecular version, S-phenyl chlorothioformate was used as the radical trap and the radical-mediated carboxylation is achieved by the exposure of alkyl iodides to radical trap in the presence of bis(tributyltin) with irradiation (Scheme 76). Methyloxalyl chloride was also used as a radical trap for alkyl radicals to form esters.



Scheme 76 Carboxylic acid derivatives used as alkyl radical traps.

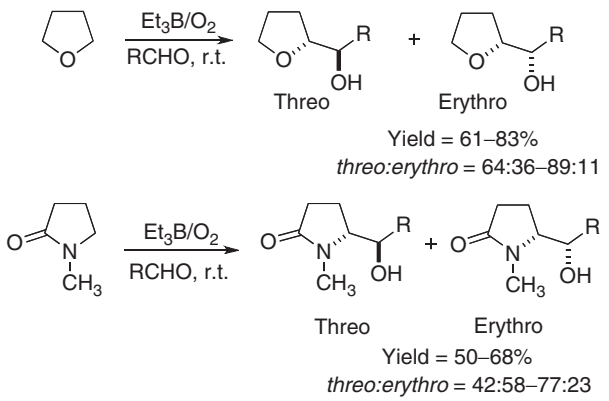
Tomioka and coworkers reported the chemoselective three-component reaction of tetrahydrofuran (THF) radical addition to aldehydes and imines.[120] It was found during these studies that THF radicals add to imines in presence of Me_2Zn/O_2 but adds to aldehydes in the presence of Et_3B/O_2 system (Scheme 77). Although the diastereomeric ratios of the products were between 3:2 and 1:1, the relative stereochemistry of the products were not shown.



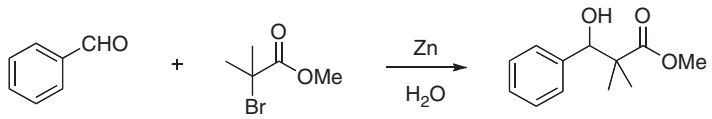
Scheme 77 Chemoselective addition of THF radical to aldehydes and imines.

Yoshimitsu and coworkers examined the intermolecular radical additions to aldehydes under triethylborane/O_2 conditions (Scheme 78).[121,122] In these studies they found that in the presence of Et_3B/O_2, ethers and acetals add to aldehydes efficiently. For example, THF adds to different aliphatic and aromatic aldehydes with good diastereoselectivity. The protocol has good ether scope too. Acyclic, cyclic, and vinyl ethers add efficiently with good stereoselectivity. The authors also studied the radical-mediated addition of tertiary amides, ureas, and amines to aldehydes. Scheme 78 shows one such addition of γ-lactam to aromatic aldehydes. Unlike ethers and lactams, amines and ureas add only with moderate selectivity.

Another useful synthetic transformation where α-acyl radicals have been added to aldehydes or ketones is Reformatsky-type reaction. The Reformatsky reaction[123] is often plagued by extended reaction times and side reactions when Zn dust is used as a reductant. In order to overcome these shortcomings, the reaction has been investigated over the past 125 years.[124–126] Although the conventional reaction is believed to proceed through an ionic pathway such as the addition of enolates to aldehydes or ketones, there have been reports that contradicts this point of view. Chan proposed a SET mechanism involving an electron transfer from the metal to α-bromoester, which results in the formation of an α-acyl radical. The radical can be trapped by the carbonyl group of the aldehyde or ketone resulting in the formation of β-hydroxy esters.[127] Alternately, Bieber et al. proposed a radical chain mechanism that does not involve hydrogen abstraction.[128] In this study, the reaction was carried out using water as solvent (Scheme 79). The yields were comparable to those obtained using anhydrous solvents.



Scheme 78 Radical addition of THF and γ-lactam to aldehydes.

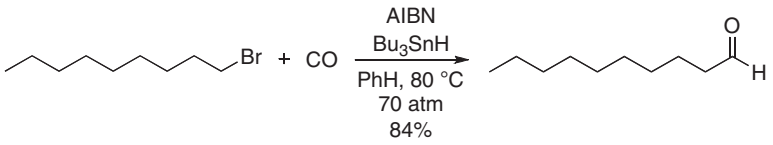


Scheme 79 Radical Reformatsky reaction in water.

4.12.3.2 Free-Radical Additions to Carbon–Oxygen Triple Bond (Carbonylation)

The first report on the reaction of carbon-centered radicals with CO appeared in 1939, when Faltings observed that acetone was formed on exposing a mixture of ethane and CO to UV light.[129] Pioneering work in this field was done by chemists at DuPont, who were mainly interested in developing a new methodology for polymer synthesis using ethylene and CO.[130] However, till the 1980s the radical carbonylation failed to attract the attention of organic chemists. With the development of radical chemistry in the 1980s, systematic studies on radical carbonylation began in 1990.[131,132]

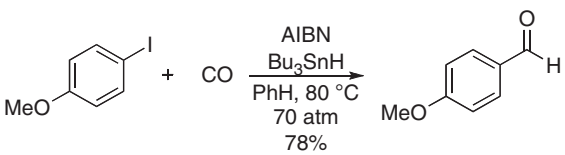
Ryu et al. reported the first efficient trapping of alkyl radicals by CO (Scheme 80).[133] Several alkyl halides were formylated using this protocol. Tributyltin hydride was used as the mediator for trapping the resultant acyl radical. In general this protocol for radical formylation requires high concentration of CO in comparison to tributyltin hydride. This avoids the premature reduction of the alkyl radical by tin hydride. Another important side reaction that is taken care of by the high concentration of CO is the decarbonylation of the acyl radical intermediate.



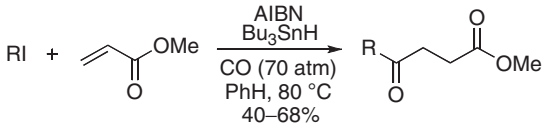
Scheme 80 Radical formylation of alkyl bromides mediated by Bu_3SnH.

Ryu et al. extended the above protocol for synthesizing other aldehydes and ketones. Even aromatic halides can be hydroformylated efficiently. The addition of acyl radicals to electron-deficient alkenes allows the synthesis of ketones (Scheme 81).[134]

Ryu and coworkers reported that intermolecular acyl radicals derived *in situ* from radical addition to CO can participate in radical conjugate addition reactions (Scheme 82).[135] High pressures of CO were required to avoid the reduction of radicals. Also it was found that use of poorer hydrogen donor such as TTMSS in place of tributyltin hydride allowed these reactions to take place at lower pressure of CO.

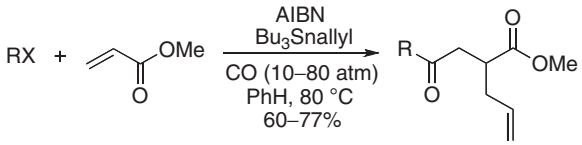


Scheme 81 Tinhydride-mediated formylation of aromatic halides.



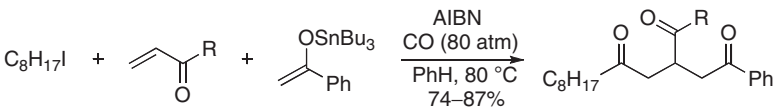
Scheme 82 Conjugate radical addition of acyl radicals.

Ryu and coworkers reported a four-component reaction by the replacement of tributyltin hydride with allyltributylstannane (Scheme 83).[136] The reaction yielded highly functionalized ketones in a single synthetic operation. Ryu and Curran also reported the use of fluorous allyltin reagents in this kind of reaction, which simplified product isolation from tin reagents.[137]



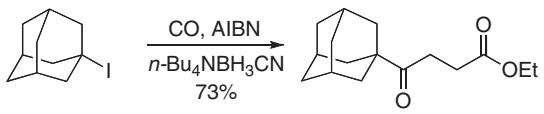
Scheme 83 Four-component reaction using radical carbonylation.

Ryu and Hosomi reported similar four-component reaction in which carbonylation of alkyl iodide followed by radical addition to α,β-unsaturated ketones or esters and the trapping of resulting α-carbonyl radical by nucleophilic stannyl enolate (Scheme 84).[138]



Scheme 84 Four-component radical carbonylation.

Recently, Ryu and coworkers reported a tin-free Giese-type reaction and related carbonylation reactions using alkyl iodides and sodium cyanoborohydride (Scheme 85).[139] In these reactions, alkyl radicals were added to electron-deficient alkenes using catalytic amount of tributyltin hydride (formed from tributyltin chloride and sodium cyanoborohydride). But in this report, Ryu et al. were able to eliminate the use of tin-source and achieve Giese-type alkylation and related carbonylations with moderate to good chemical efficiency (Scheme 85).

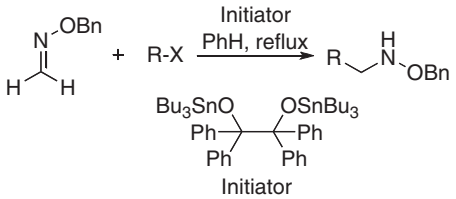


Scheme 85 Tin-free Giese-type carbonylation.

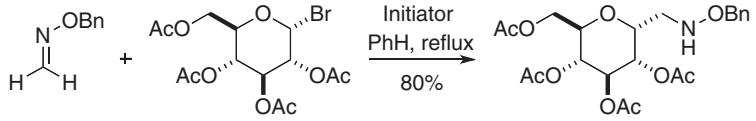
4.12.3.3 Free-Radical Addition to Carbon–Nitrogen Double Bonds

Owing to the presence of a simple methylene group which is free from stereochemical considerations, radical additions to formaldoximes were the first to be exploited in synthesis. Hart reported one carbon homologation of alkyl halides to corresponding hydroxylamines using addition of alkyl radicals to oxime ethers (Scheme 86).[140] In this report, bis(trialkylstannyl) benzopinacolate was used as the source of trialkyltin radicals. The normal Bu_3SnH/AIBN conditions were not effective for this transformation. Several alkyl halides added to the oxime ether in 56–84% yield. Functionalized alkyl halides are also competent in this reaction. Bhat and coworkers[141] have extended this methodology to intermolecular radical coupling of nucleosides and formaldoximes. Intermolecular reductive coupling of formaldoxime and carbonyl compounds promoted by SmI_2 has been reported by Inanaga's group.[142]

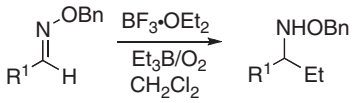
Naito and coworkers were the first to report radical addition reactions to oxime ethers other than formaldoximes (Scheme 87).[143] Ethyl radical formed from the reaction of triethylborane and oxygen adds to aldoximes to form amines. Lewis acid $BF_3.OEt_2$ was required for the radical addition. Selective 1,2-addtion product was formed when an unsaturated oxime ether (Ph-CH═CH–CH═NOBn) was used as the substrate.



R-X	Yield (%)
$CH_3(CH_2)_7I$	77
$C_6H_{11}I$	76
$C_6H_{11}Br$	56
Cyclohexylphenylselenide	78
t-BuBr	84
PhI	67



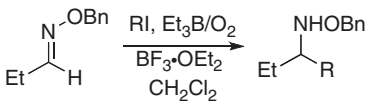
Scheme 86 Benzopinacolate-promoted radical addition to formaldoxime.



R^1	Yield (%)
Et	95
Ph	93
2-MeO-Ph	93
2-HO-Ph	41
4-HO-Ph	96
3-thienyl	57
PhCH=CH	62

Scheme 87 Ethyl radical addition to various aldoxime ethers.

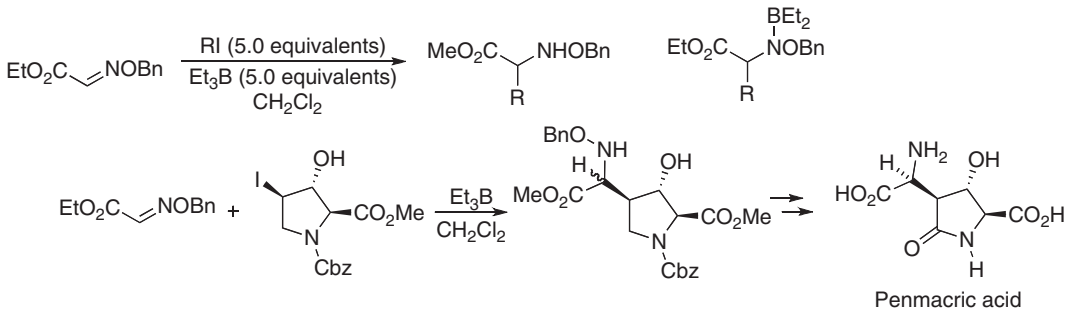
Under the conditions of Et_3B/O_2, various alkyl radicals add to propionaldehyde oxime ether with moderate to good chemical efficiency (41–98% yields). The main disadvantage of this method is that it cannot be applied to primary alkyl radical addition because of inefficient iodine transfer by the Et_3B system (Scheme 88).



R	Yield (%)
t-Bu	98
i-Pr	76
Cyclohexyl	58
Adamantyl	41

Scheme 88 Alkyl radical additions to propionaldoxime ether.

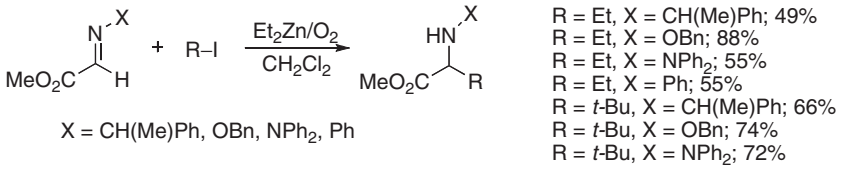
Glyoxylic imines are useful starting materials for the synthesis of natural and unnatural amino acids. Naito and coworkers reported the addition of secondary and tertiary radicals to glyoxylic oxime ether (Scheme 89).[144] Unlike normal ethers, glyoxylic oxime ethers are more reactive. The electron-withdrawing ester group activates the C=N bond toward radical addition. The reaction under normal stannyl-radical-mediated conditions yielded protected α-amino esters as products in good yield. In the



Scheme 89 Radical addition to glyoxylic imine ethers: Synthesis of penmacric acid.

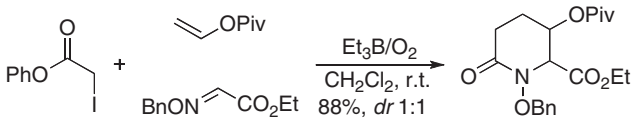
absence of Bu_3SnH, the reaction proceeded via iodine atom transfer. The proposed reaction mechanism involves the formation of intermediate N-boryl bond which is converted into an NH bond during workup. Recently, NMR studies[145] have corroborated the formation of such intermediate during the reaction. Using this general procedure, Naito synthesized penmacric acid and *epi*-penmacric acid (Scheme 89).[146]

Bertrand and coworkers have used diethylzinc as an activator and chain-transfer reagent in the addition of alkyl radicals to unactivated amines, glyoxylic oxime ethers, and hydrazones (Scheme 90).[147] On subjection to controlled addition of Et_3B and Et_2Zn, several substrates gave identical results establishing a strong similarity between mode of initiation and chain transfer. This method is applicable only to secondary and tertiary alkyl radical addition.



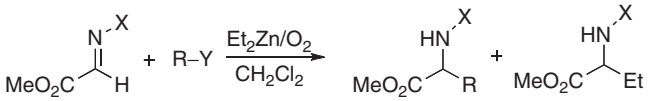
Scheme 90 Diethylzinc-mediated radical addition to C═N.

Landais described an intramolecular free-radical [2 + 2 + 2]-type process based on the addition of nucleophilic radicals onto oximes (Scheme 91). This allowed the elaboration of fused-ring piperidinones from allylsilanes possessing an oxime moiety. The silicon substituent was used as a stereocontrol element, which was particularly efficient in this context. The process involved an intermolecular addition of an electron-poor radical species onto the double bond of the chiral allylsilane, which was followed by a 5-*exo*-trig cyclization onto the oxime. The cascade was completed by the formation of the amide bond by nucleophilic attack of the amine onto the ester function.[148,149] An intermolecular version was also devised, the three-component process giving rise to a series of substituted piperidinones in modest to good yields, with the generation of two C–C and one C–N bonds in a one-pot process.[150] With disubstituted oximes, no diastereocontrol was however observed.



Scheme 91 [2 + 2 + 2]-type cyclizations based on radical addition to oximes.

Bertrand also used phenylorganotellurium compounds as the source of radical in Et_2Zn-mediated radical addition to C═N bond.[148b] It was shown that the reaction of phenylalkyl tellurides with ethyl radical is twice as fast as their iodide counterparts. This greatly enhances the chemoselectivity and reaction efficiency (Scheme 92).



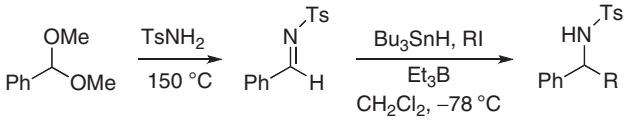
X	R-Y	Prod.(%)	Ethyl (%)
CH(Me)Ph	*i*-PrI	73	27
CH(Me)Ph	*i*-PrTePh	90	10
NPh_2	*i*-PrI	76	34
NPh_2	*i*-PrTePh	100	0
NPh_2	*i*-PrTePh	93	7

Scheme 92 Comparison of alkyl radical precursors toward radical addition to C═N bonds.

Naito and coworkers have examined *N*-sulfonylimines as radical acceptors.[151] Under tin-mediated radical conditions, alkyl radicals add to sulfonyl imines (43–80%). This reaction was extended to one-pot synthesis of amine derivatives starting from the acetal (Scheme 93).

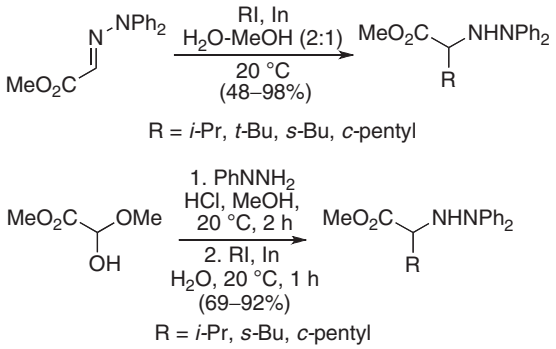
From economic and environmental point of view, organic transformation in water has received greater attention. Carbon–carbon bond forming reactions in aqueous medium is challenging. Thus indium-mediated carbon–carbon bond forming reactions have received interest.[152] Naito and coworkers reported indium-mediated addition of alkyl radicals to oxime ethers, hydrazones, and sulfonylimines.[153] The indium-mediated radical addition was extended to one-pot synthesis of amines starting from the corresponding hemiacetal (Scheme 94).

A mechanism for the indium-mediated reaction has been proposed. SET from indium results in the formation of an alkyl radical, which then adds to glyoxylic hydrazone to form an intermediate radical (Scheme 95). A second SET from indium metal to the radical results in the formation of anion, which on proton abstraction from water yields the product amine.

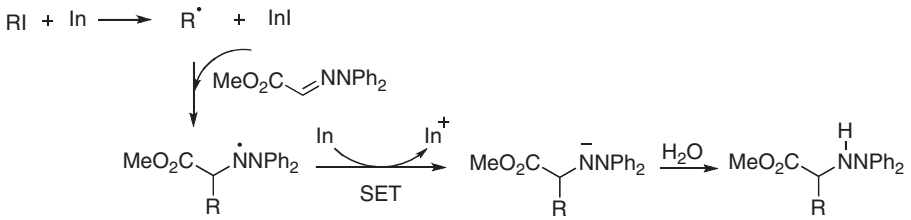


R	Prod. (%)
i-Pr	78
c-hexyl	77
c-pentyl	56
s-Bu	43

Scheme 93 Radical addition to N-sulfonylimines.

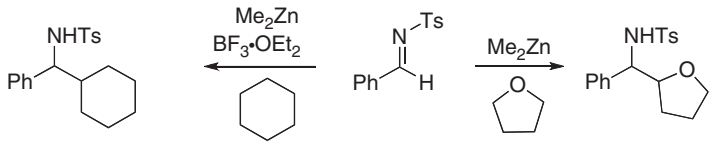


Scheme 94 Indium-mediated radical additions in water.



Scheme 95 Mechanism of indium-mediated radical additions.

Tomioka and coworkers have developed a new methodology for the direct addition of ether to *N*-sulfonylimines (Scheme 96).[154] In this reaction, Me_2Zn in the presence of air forms methyl radical. Methyl radical can abstract hydrogen atom from THF to form 2-tetrahydrofuryl radical which then adds to C═N bond to form the adduct. This reaction was extended to the addition of cycloalkyl radical across C═N bond. Cycloalkyl radical can be directly generated from cyclohexane using dimethylzinc. Unlike the addition of ether radicals, this reaction requires the addition of Lewis acid.[157b]

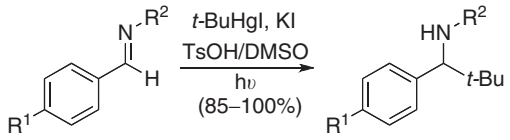


Scheme 96 Dimethylzinc-mediated radical addition.

Radical addition to unactivated imines was first reported by Russell et al. (Scheme 97).[155] In this report, *t*-butyl radical generated from *t*-BuHgI was added to benzylidene anilines to form adducts. The addition of acids such as *p*-toluenesulfonic acid (PTSA), promotes the radical chain process by activating the substrate and increasing the electron affinity of the intermediate radical.

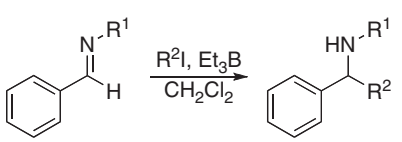
Substituents on the N-atom of the imines have a dramatic effect on the rate and efficacy of the radical additions. After careful studies with different N-substituents, Takemoto et al.[156] concluded that an *o*-phenolic hydroxyl group has a remarkable effect on the rate and efficiency of the reaction (Scheme 98).

Although nitrones are used extensively as spin traps, it has hardly been used in radical reactions. VallÅe and coworkers reported the SmI_2-mediated coupling of nitrones with aldehydes and ketones.[157] Acyliminium ion generated by the low temperature electrochemical oxidation of 2-trimethylsilylpyrrolidine can be used as traps in radical reactions. Yoshida and Suga reported the addition of primary alkyl radical to acyliminium ion to give adducts (Scheme 99).[158]

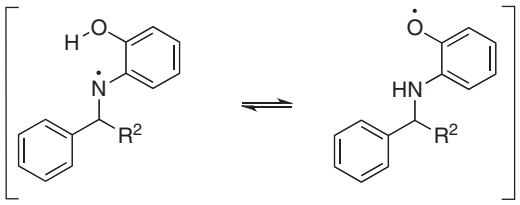


R^1 = H, Cl, Br, CN, Me, OMe
R^2 = Ph, *p*-CN-Ph

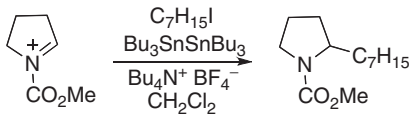
Scheme 97 Radical addition to unactivated imines.



R^1	R^2	Yield (%)
BOC	Et	23
CO_2Me	Et	21
Ph	Et	40
2-HO-Ph	Et	80
2-HO-Ph	*i*-Pr	90

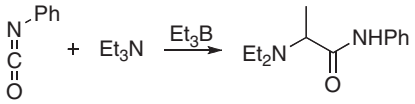


Scheme 98



Scheme 99 Free-radical addition to acyliminium ions.

Isocyanates are also competent substrates in radical reactions. Tanaka and Yoshimitsu recently reported the use of isocyanate as a radical trap in carbon–carbon bond forming reactions (Scheme 100).[159]



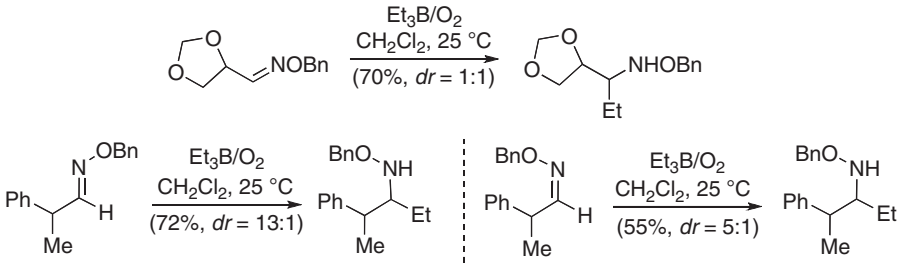
Scheme 100 Radical addition to isocyanates.

4.12.3.3.1 Diastereoselective radical addition to carbon–nitrogen double bonds

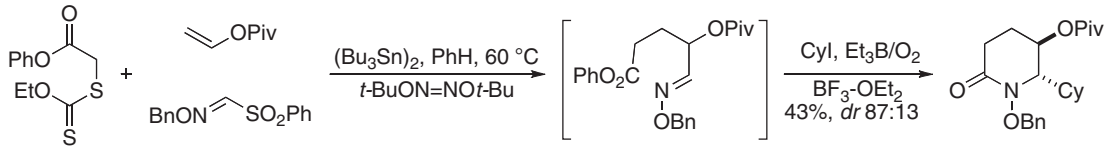
4.12.3.3.1.1 Substrate-controlled intermolecular additions

There are only few examples of substrate-controlled intermolecular radical additions to imine derivatives. Naito et al.[146b] reported ethyl radical additions to acetonide of glyceraldoxime. Although the yields were high, there was no diastereoselectivity in the reaction (Scheme 101). But oxime ethers with different double bond geometry gave the addition products in high selectivity. The relative stereochemistry in the product was not assigned. These examples show the dependence of E/Z isomerism of oxime ethers on the diastereoselectivity of the reaction.

Closely related additions of radical species to oximes have been reported by Landais to prepare piperidinones with reasonable level of diastereocontrol (Scheme 102).[150] The one-pot process involved the elaboration of the oxime precursor through a three-component reaction, which was followed by the addition of an alkyl iodide in the presence of Et_3B and BF_3-OEt_2. Piperidinones with *trans* relative configuration were thus obtained in modest yields.

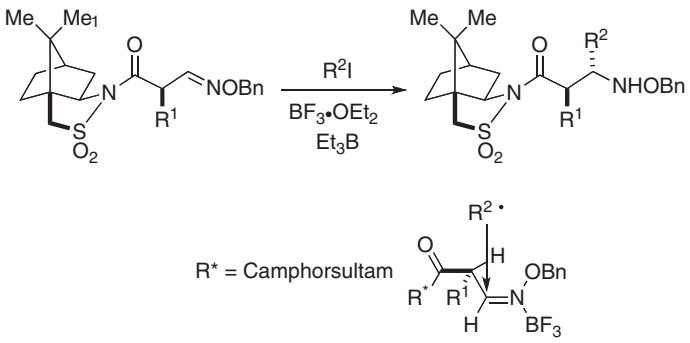


Scheme 101 Substrate-controlled diastereoselective radical addition.



Scheme 102 Substrate-controlled diastereoselective radical addition.

Naito and coworkers have investigated radical additions to chiral oxime ethers (Scheme 103).[160] In the presence of Lewis acid $BF_3.OEt_2$, under tin-free conditions, the reaction proceeded smoothly to give adducts. The diastereoselectivities of these reactions were very high. The camphorsultam chiral auxiliary had no effect on the stereoselectivity of the reaction: when compound (R^1 = H) was subjected to reaction conditions, only 5% *de* was obtained. In contrast, when compound (R^1 = Bn) or compound (R^1 = PNB) was subjected to ethyl radical additions, *de*'s up to 95% was obtained. Other secondary alkyl halides also added to oxime ethers with high stereoselectivity. Isobutyl radical added with low chemical efficiency because of competitive ethyl radical addition. The release of $A_{1,3}$ strain in conformation showed results in a transition state where R^1 blocks one face of C=N double bond leading to high diastereoselectivities.



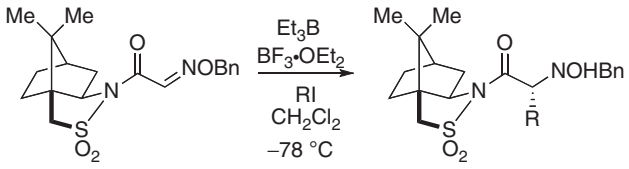
R^1	R^2	Prod (%)	%*de*
H	Et	95	5
Bn	Et	99	95
PNB	Et	43	95
H	*i*-Pr	70	95
H	*c*-hexyl	57	95
H	*c*-pentyl	59	95
H	*s*-Bu	50	95
H	*i*-Bu	20	95
Bn	*i*-Pr	40	95

Scheme 103 Oppolzer's camphorsultam-controlled radical addition to glyoxylic oxime ether.

4.12.3.3.1.2 Chiral auxiliary-controlled diastereoselection

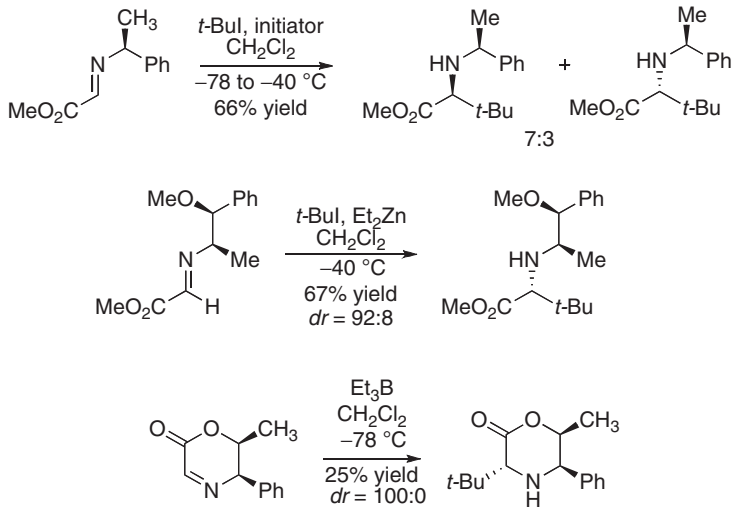
Chiral auxiliary-controlled diastereoselective radical addition to C=N bonds was first reported by Naito.[161] In this report, the readily available Oppolzer's camphorsultam was used as the chiral auxiliary. The substrate when subjected to radical addition conditions using triethylborane as the initiator, gave adducts in good yields and very high diastereoselectivities (Scheme 104). Lewis acids were found to impact chemical efficiency as well as the diastereoselectivity of the reaction. Among several Lewis acids screened, $BF_3.OEt_2$ in dichloromethane gave optimum yields and selectivity.

A variety of chiral auxiliaries can be attached to the nitrogen of the imines. Bertrand and coworkers studied radical addition to glyoxylic imines possessing a chiral auxiliary at the N-atom (Scheme 105).[162] When phenethylamine-derived imine was subjected to *t*-butyl radical addition, under triethylborane initiation, two diastereomers were formed in a 7:3 ratio. Diastereoselectivity could be enhanced by using an imine derivative that is capable of chelating a Lewis acid. Hence using Zn(II) as a Lewis acid and norephedrine-derived imines as the substrates, Bertrand and coworkers achieved very high diastereoselectivities in the addition of *t*-butyl and cyclohexyl radicals to the acyclic imines (Scheme 105).[163] Similarly, when a cyclic imine was subjected to the same reaction conditions, only one diastereomer was formed.



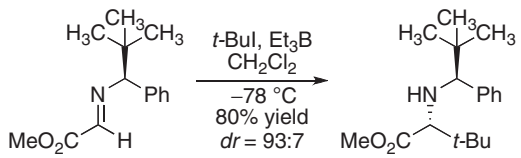
R	Yield (%)	%*de*
Et	80	95
i-Pr	80	96
i-Bu	83	97
c-hexyl	70	96
s-Bu	69	>98
t-Bu	57	>98
$Cl(CH_2)_4$	59	>98

Scheme 104 Diastereoselective radical additions to chiral oxime ethers.



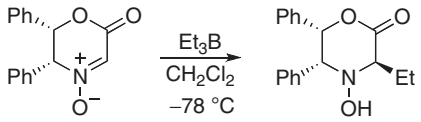
Scheme 105 Diastereoselective radical addition to chiral cyclic and acyclic glyoxylate imines.

Recently, Trehan and coworkers found that changing the sterics on the N-atom could increase the diastereoselectivity in the acyclic system. Using the bulky imine substrate one could add different alkyl radicals with very high selectivity (Scheme 106).[164]



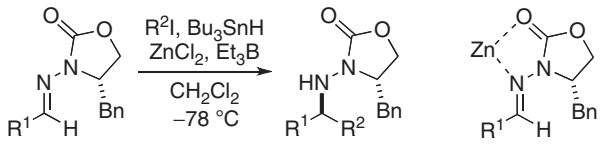
Scheme 106 Diastereoselective diethylzinc-mediated radical addition to chiral acyclic glyoxylate imines.

Naito reported radical additions to cyclic nitrones (Scheme 107).[165] When the chiral cyclic nitrone was subjected to reaction with Et_3B, a single diastereomeric adduct was obtained in 66% yield.



Scheme 107 Stereoselective ethyl radical additions to cyclic nitrones.

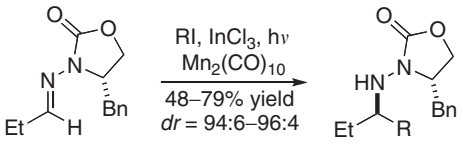
Friestad and coworkers developed novel chiral *N*-acylhydrazones as substrates in stereoselective radical addition reactions.[166] The hydrazones, when subjected to radical reaction conditions gave adducts with high stereoselectivity (Scheme 108).[167] The high control of diastereoselectivity in the reaction was attributed to the formation of a chelate. In such an intermediate, the C–N bond is fixed in the ring and hence the N–N bond rotation is restricted because of formation of a five-membered chelate with the Lewis acid. The benzyl group on the auxiliary restricts the approach of nucleophile to one face of the C═N double bond.



R^1	R^2	Yield (%)	%*de*
Et	*i*-Pr	60	98
Ph	*c*-hexyl	28	94
Et	*c*-pentyl	59	92
Et	*t*-Bu	54	90
Ph	*i*-Pr	42	98
Ph	*c*-hexyl	30	97
Ph	*c*-pentyl	59	92
Ph	*t*-Bu	83	86

Scheme 108 Stereoselective radical addition of chiral N-acylhydrazones.

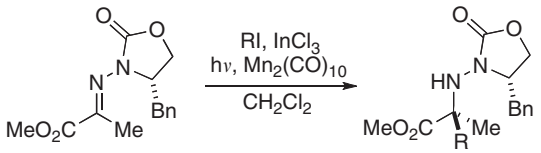
Friestad and coworkers also developed a novel synthetic procedure for the highly diastereoselective addition of primary alkyl radicals to chiral *N*-acylhydrazones (Scheme 109).[168] $Mn_2(CO)_{10}$-mediated photolytic addition of primary alkyl radicals in the presence of $InCl_3$ afforded adducts with high selectivity.



R = Me, Et, Pr, *n*-Bu, *n*-pentyl

Scheme 109 Manganese-mediated highly diastereoselective addition of primary alkyl radical addition.

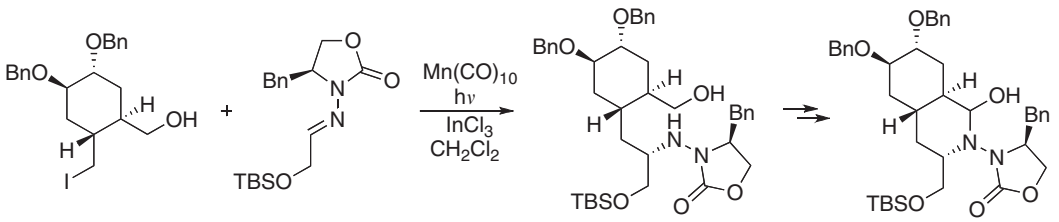
Recently, Friestad and coworkers demonstrated that radicals could be added to hydrazones derived from ketones with moderate to good diastereoselectivity (Scheme 110).[169] In presence of $InCl_3$ as a Lewis acid, ethyl, and *iso*propyl radical added to hydrazone to give products with moderate to good diastereoselectivity.



R = Et; 79%; *dr* = 7:3
R = *i*-Pr; 85%; *dr* = 92:8

Scheme 110 Stereoselective radical additions to chiral hydrazone derived from a ketone.

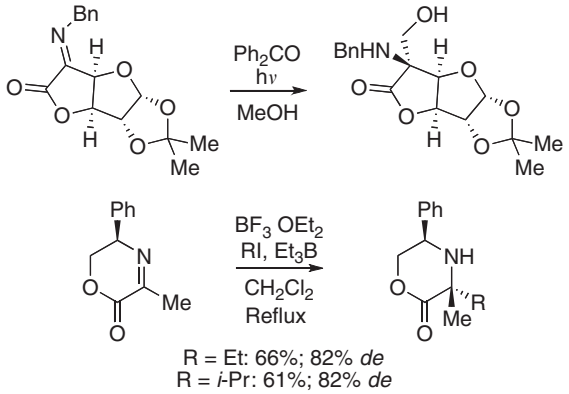
During studies directed toward the formal synthesis of quinine alkaloids, Friestad and coworkers used Mn-mediated alkyl radical addition to chiral hydrazones as the key step. Many functionalized alkyl halides can be added to chiral *N*-acylhydrazones in presence of $InCl_3$ and $Mn_2(CO)_{10}$. For instance, a primary radical derived from an alkyl iodide added to the chiral hydrazone (Scheme 111)[170] to afford the product as a single diastereomer in 93% yield. This product could be converted into perhydroisoquinoline in subsequent steps.



Scheme 111 Perhydroisoquinoline synthesis by Mn-mediated radical additions to hydrazones.

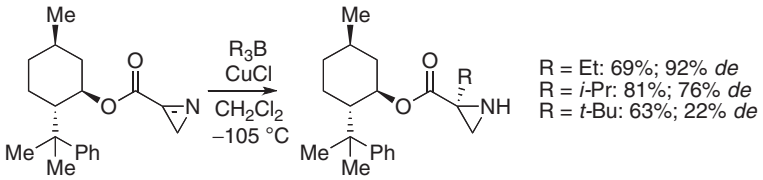
Although the stereoselective addition of radicals to aldoximes and its derivatives has been developed recently, the corresponding addition of radicals to ketoximes has been poorly developed. The main reason being the poor electrophilicity of the

C═N bond in ketoximes and less control over the stereoisomerism of C═N double bonds. Alonso et al. reported the first stereoselective addition of radicals to cyclic ketoximes (Scheme 112).[171]



Scheme 112 Stereoselective radical addition to ketimines.

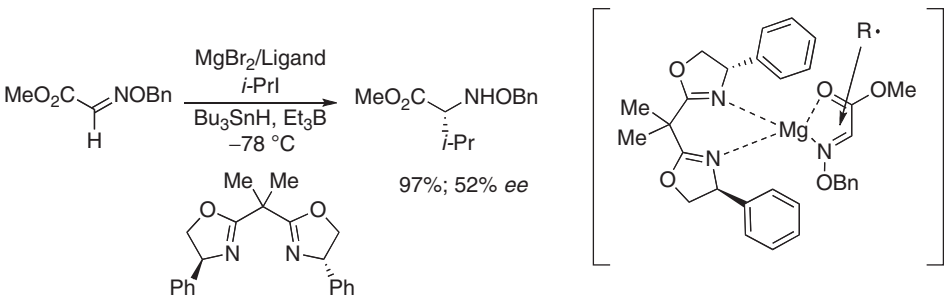
Takemoto and Miyabe reported the addition of alkyl radicals to hydrazones derived from pyruvic acid and isatin using triethylborane as an initiator.[172] The chiral ketimine when subjected to Et_3B-mediated alkyl radical addition in dichloromethane formed adducts in good diastereomeric excess. Somfai et al. reported the addition of alkyl radicals to azirine-3-carboxylate under tin-free conditions. In this reaction, 8-phenylmenthol was used as a chiral auxiliary. In presence of Cu(I) as the Lewis acid, alkyl radicals add smoothly to yield aziridines (Scheme 113).[173]



Scheme 113 Diastereoselective addition to azirine-3-carboxylates.

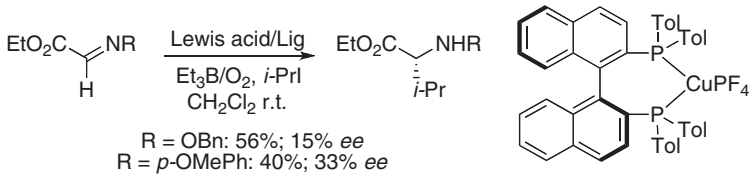
4.12.3.3.2 Enantioselective free-radical additions to carbon–nitrogen double bonds

Even though radical additions to imines have been very well studied over the last two decades, there has only been handful of reports on catalytic enantioselective version of such a process. In 2000, Naito reported the first CLA-catalyzed enantioselective addition of alkyl radicals to glyoxylic imine ethers (Scheme 114).[164b] Among the Lewis acids screened with the combination of a chiral ligand, only $MgBr_2$ gave reasonable *ee*'s for the addition of isopropyl radical. A tetrahedral model has been proposed to explain the observed selectivity for the reaction.



Scheme 114 Chiral Lewis acid catalyzed enantioselective addition of isopropyl radical.

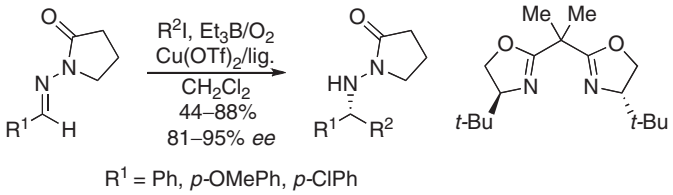
Halland and Jørgensen used a CLA derived from Cu(I) and 2,2′-bis(ditolylphosphino)-1,1′-binaphthyl (Tol-BINAP) ligand for the enantioselective addition of isopropyl radical to glyoxylate imine derivatives (Scheme 115).[174] Although this reaction was



Scheme 115 Enantioselective radical addition catalyzed by Cu(I)-BINAP.

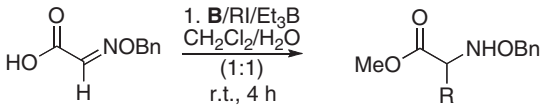
done under tin-free conditions, it was plagued by competitive ethyl radical addition. Also, only alkyl iodides could be used as the radical source. The observed enantioselectivity was also very low.

Friestad reported enantioselective radical additions to *N*-acylhydrazones in the presence of CLAs (Scheme 116).[175] Using Cu $(OTf)_2$ and *t*-Bu box ligand as the CLA system, they were able to obtain very high enantioselectivities for various alkyl radical additions (81–95% *ee*). The amount of catalyst had a significant impact on enantioselectivity. When the amount of the CLA was reduced from 100 mol% to 10 mol%, the *ee* for the isopropyl addition product dropped from 90% to 48%.

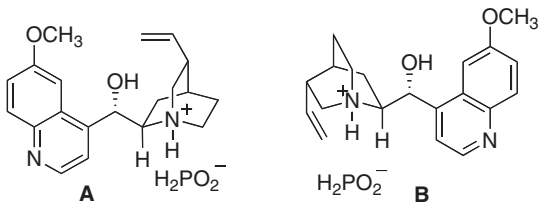


Scheme 116 Enantioselective radical additions to hydrazones.

Jang and coworkers reported enantioselective radical additions to glyoxylate oxime ethers using chiral quaternary ammonium salts of hypophosphorous acid in aqueous medium (Scheme 117).[176] The quaternary ammonium hypophosphites **A** and **B** were used as catalysts in the reaction. The oxime ether generated *in situ* was allowed to react with *i*-PrI in a biphasic mixture of CH_2Cl_2 and water in presence of **A** or **B** using Et_3B/O_2 as radical initiator. Optimum yields were obtained with 2 equivalents of chiral quaternary ammonium hypophosphite **B**, 5.0 equivalents of *i*-PrI, and 0.5 equivalent of Et_3B in aqueous CH_2Cl_2. The *er* for the reaction was determined after converting the product acid into corresponding ester. The addition takes place smoothly under mild conditions and gave high enantioselectivities. When **A** was used as the catalyst, lower enantiomeric ratios were obtained for the addition of primary and secondary alkyl radicals (*er* of 62:38 as opposed to 21:79 for *i*-Pr, 58:42 for *n*-octyl and 72:28 for *c*-hexyl).



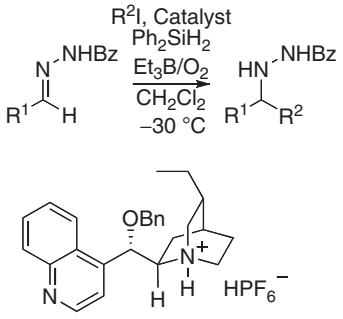
R	Acid (%)	Ester (%)	*er* of Ester R : S
i-Pr	83	80	21:79
c-hexyl	80	81	21:79
t-Bu	60	83	1:>99
1-Ad	45	82	1:>99
n-octyl	50	85	40:60



Scheme 117 Enantioselective radical addition in the presence of quaternary ammonium salts in biphasic media.

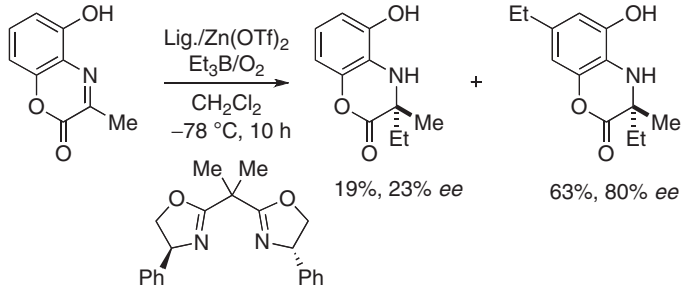
Recently, Jang reported enantioselective radical additions to hydrazones using protonated cinchona alkaloids. Among the cinchona alkaloids screened, a catalyst capable of H-bonding to the substrate gave promising results. The reaction showed good substrate scope. Several hydrazone substrates were easily converted into the corresponding adducts in good yield and high enantioselectivity (Scheme 118).[177] Primary, secondary, and tertiary alkyl radicals add to C═N double bond effectively with high enantiocontrol.

Takemoto et al. have examined CLA-catalyzed enantioselective radical additions to ketimines.[157] Several Lewis acids in combination with chiral box ligands were screened for ethyl radical addition to ketimine. In the presence of $Zn(OTf)_2$ and box ligand, the product (19%, 23% *ee*) and a diethylated compound (63%, 80% *ee*) were formed (Scheme 119). It was found that the



Entry	R^1	R^2	Yield (%)	*ee* (%)
1	4-ClPh	*i*-Pr	81	99
2	4-MeC(O)Ph	*i*-Pr	80	99
3	4-NO_2-Ph	*i*-Pr	81	99
4	Ph	*i*-Pr	81	99
5	4-OH-Ph	*i*-Pr	79	98
6	4-OMe-Ph	*i*-Pr	80	98
7	4-MeC(O)NH-Ph	*i*-Pr	77	99
8	4-Et-Ph	*i*-Pr	81	99
9	$CH_3(CH_2)_6$	*i*-Pr	72	80
10	4-F-Ph	*c*-hexyl	80	99
11	4-F-Ph	*t*-Bu	71	99
12	4-F-Ph	1-adamantyl	70	99
13	4-F-Ph	*n*-octyl	55	81

Scheme 118 Enantioselective radical addition to hydrazones in the presence of quaternary ammonium salts.



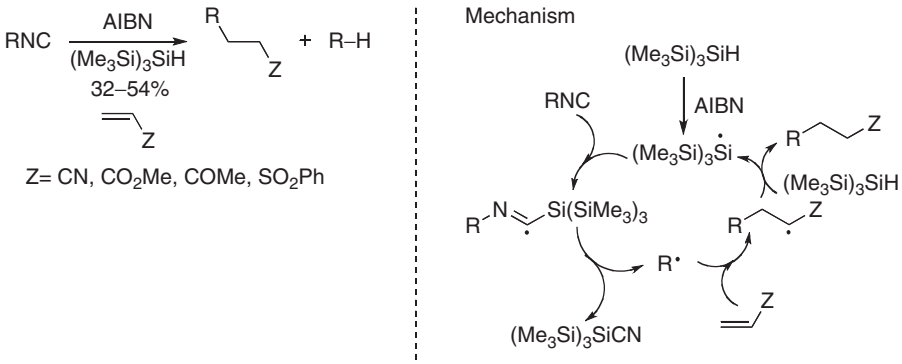
Scheme 119 Enantioselective radical additions to ketimines.

rate of radical addition was very slow and thus bulky CLAs suppressed the trapping of the intermediate radical by Et_3B. The accumulation of an intermediate radical and its coupling with ethyl radical results in the formation of the diethylated compound.

4.12.3.4 Free-Radical Additions to Isonitriles

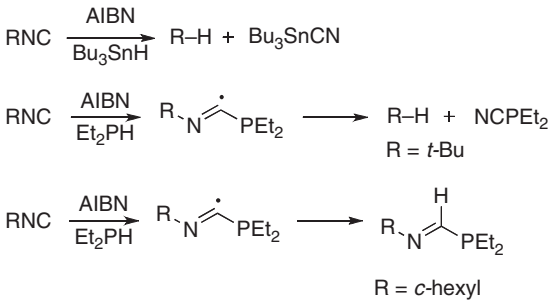
Imidoyl radicals are important synthetic intermediates that can undergo inter- and intramolecular radical additions onto olefins, alkynes, aromatics, etc. Hence they are often used in synthesis of nitrogen-containing heterocycles such as indoles, pyrrolidines, and quinolines. One of the known methods of generating imidoyl radicals is by the addition of radicals to isonitriles and isothiocyanates.[178]

Shono et al.[179] suggested the intermediacy of imidoyl radicals when cyclohexyl isonitrile was allowed to react with radical sources such as benzoylperoxide. These radicals add to the carbon atom of the isonitrile to furnish imidoyl radicals, which can then abstract a hydrogen atom or can be trapped by radical acceptors to form imines and its derivatives (Scheme 120).



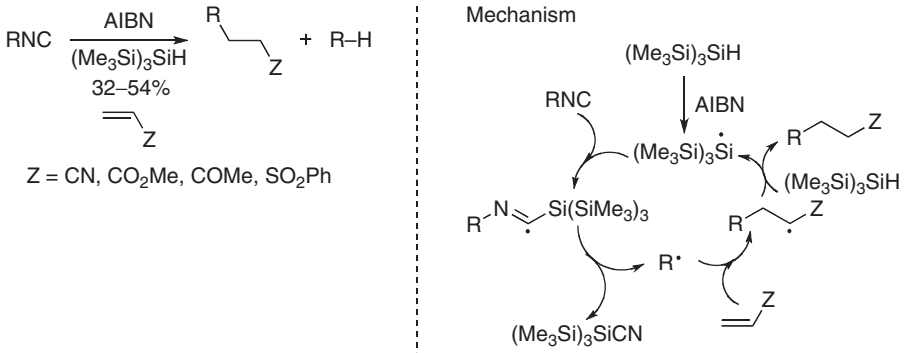
Scheme 120 Radical additions to isonitrile to form imidoyl radicals.

Saegusa et al. reported the addition of radicals to isonitriles initiated by the addition of tributyltin radical (Scheme 121).[180] The reaction of tributyltin hydride and AIBN with isonitriles resulted in the formation of alkanes and tributyltin cyanide. Similar results were obtained for the addition of phosphinyl radicals.[181] In the case of phosphinyl radical addition, the final products depended on the nature of the isonitrile used. When *tert*-butyl and benzyl isocyanides were used as radical traps, diethylcyanophosphine along with the corresponding alkanes (isobutane and toluene) were obtained as products. But when cyclohexyl or *n*-hexyl isocyanides were used, diethylformimidoylphosphines were obtained (Scheme 121). This shows that hydrogen atom transfer may compete with β-fragmentation in the absence of groups that can be released as stable radicals.



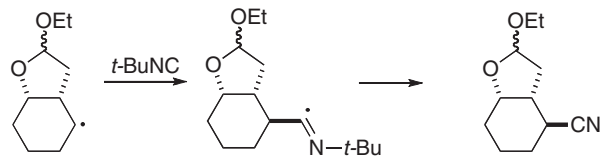
Scheme 121 Addition of tin and phosphorous centered radicals to isonitriles.

The first synthetic application of radical addition to isonitrile was reported by Barton and coworkers.[182–184] The fact that imidoyl radicals undergo β-fragmentation was used by Barton et al., in the deamination of steroidal amines and aminoglycosides. Giese and coworkers used the alkyl radicals formed from the fragmentation of imidoyl radicals in carbon–carbon bond forming reactions (Scheme 122).[185] The protocol can be applied to various isocyanides and also several electron-deficient alkenes were used as traps for imidoyl radicals. The reactions were characterized by moderate yield (32–54% yield) of the desired product accompanied by hydrosilylated product (22–55%). The mechanism of this fragmentation/addition reaction is also shown in Scheme 122.



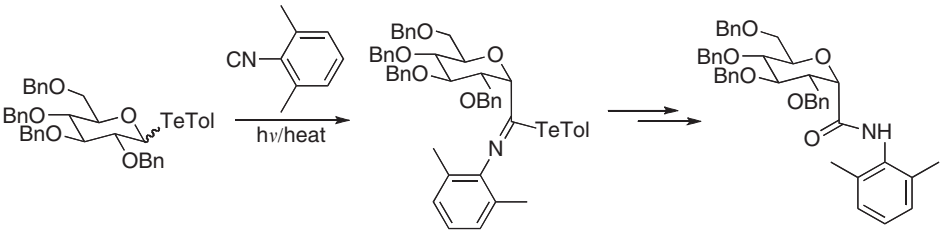
Scheme 122 Imidoyl radical fragmentation/addition reactions.

Stork and coworkers used fragmentation reactions of imidoyl radicals to synthesize nitriles.[186] Alkyl radicals generated from cyclization of bromoacetals can be trapped by *tert*-butyl isonitrile to furnish nitriles in good yield (Scheme 123).



Scheme 123 Synthesis of nitriles from imidoyl radicals.

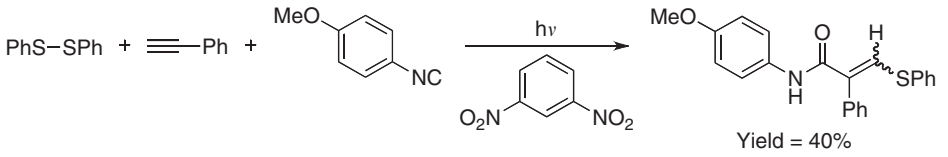
Yoshida and coworkers have investigated reaction between tellurides and isonitriles. In one study, the telluroglycosides under thermal or photolytic conditions generate radicals that add to isonitrile to form 1-telluroimidoyl glycoside (from formation of imidoyl radical followed by tellurium transfer) (Scheme 124).[187] This intermediate can be converted into the corresponding



Scheme 124 Synthesis of carbamoylglycoside by radical additions to isonitriles.

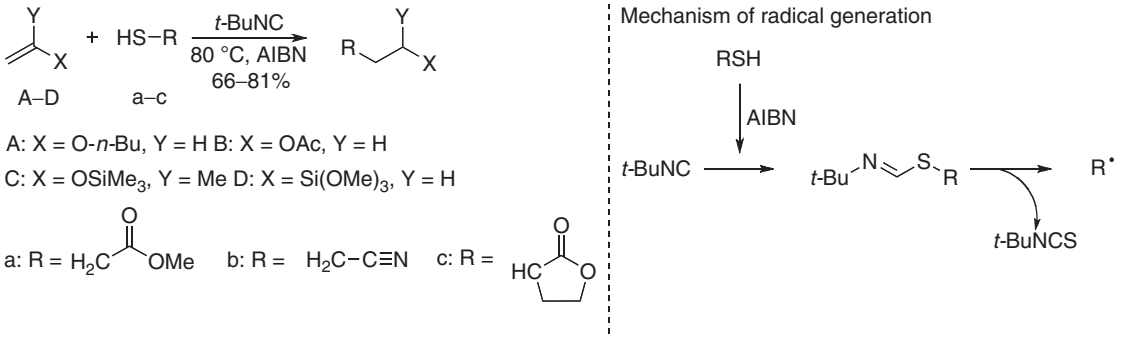
imidic esters by electrochemical oxidation followed by acid hydrolysis to carbamoylglycoside. Yoshida et al. reported a three-component reaction between silyltellurides, isonitriles, and imines. Using this method the authors achieved diversity-oriented synthesis of α-aminoacid derivatives.[188]

Nanni et al. examined a three-component reaction between aryl disulfides, alkynes, and isonitriles (Scheme 125).[189] The reaction involves photolytically generated sulfanyl radical addition to alkynes resulting in vinyl radical, which is then trapped by isonitrile to form an imidoyl radical. The resultant imidoyl radical was scavenged by *m*-dinitrobenzene resulting in the formation of β-arylthio acrylamides in moderate yields as a mixture of E and Z isomers.



Scheme 125 Three-component radical cascade.

Nanni and coworkers have developed a novel tin-free procedure for alkyl radical generation (Scheme 126).[190] Using this protocol the authors achieved tin-free defunctionalization of thiol-based sugars. Several alkyl radicals have been generated by this protocol at a relatively low temperature. This method can be an appealing alternative for stannane/silane-mediated radical reactions.



Scheme 126 Tin-free protocol for alkyl radical generation.

4.12.4 Conclusions

The process of radical additions to carbon–carbon as well as carbon–heteroatom multiple bonds are described. Radical additions involving cyclizations are not described in this review. Although the radical addition reactions surveyed in this review are more inclined toward stereoselective C–C bond-forming processes, advancement in such methodologies over the past decade or so is remarkable. With the well-studied Lewis acid-catalytic systems and rapidly developing organocatalytic systems, a high degree of stereocontrol can be achieved in intermolecular radical addition process. The C–C bond-forming process involving radical addition reactions would complement ionic reactions in meeting the ever-increasing demand for the development of novel synthetic methodologies for synthesizing complex molecular structures.

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4.13 Radical Cyclizations and Sequential Radical Reactions

BM Loertscher and SL Castle, Brigham Young University, Provo, UT, USA

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Glossary

Atom transfer radical cyclization A ring-forming process in which both the atoms involved in a given bond undergo addition to a radical acceptor.

Oxidative radical cyclization A ring-forming reaction in which the key radical species is generated via an oxidative process (i.e., a C–H bond homolysis).

Radical acceptor An unsaturated functional group that is attacked by a free radical species during a cyclization or intermolecular addition step.

Radical-polar crossover reaction A process containing a key step in which a radical intermediate is transformed into a polar intermediate.

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Reductive radical cyclization A ring-forming reaction in which the key radical species is generated via a reductive process (i.e., a C–X bond homolysis).

4.13.1 Introduction

In recent decades, the perception of radical reactions has evolved significantly. Once considered esoteric transformations with marginal preparative value, radical processes now occupy a prominent position in the field of organic synthesis. Radical reactions offer many advantages to practitioners of synthesis, such as good functional group tolerance due to essentially neutral conditions, excellent control of stereo- and/or regiochemistry (especially in cyclizations), and amenability to incorporation into tandem or cascade processes. Although the heavy reliance of radical chemistry on toxic organotin reagents was once considered a significant drawback, the discovery of numerous tin-free radical reactions has rendered the field more environmentally friendly. On the basis of these and other exciting findings, the future of radical chemistry appears to be bright.

The purpose of this chapter is to highlight noteworthy recent developments in the areas of radical cyclizations and sequential radical reactions. To focus on the current state of the art, coverage is concentrated on work that has been published since 2005. Owing to the vast body of literature in this field, it is not possible to include all of the published examples. Rather, the goal is to summarize the most useful methods that are of contemporary interest to the synthetic community. Accordingly, emphasis has been placed on stereoselective reactions, tin-free processes, and transformations affording products that are difficult to obtain efficiently by other means. Because new methodology is often validated by its use in the construction of natural products or other complex molecules, a section containing notable examples of radical cyclizations and sequential radical reactions in total synthesis is included. For a more in-depth coverage of individual aspects of these topics, the reader may consult one of the many books[1] or recent reviews[2–25] (*see* Chapter 4.12) covering various facets of radical chemistry.

4.13.2 Tin-Free Cyclizations of Carbon-Centered Radicals

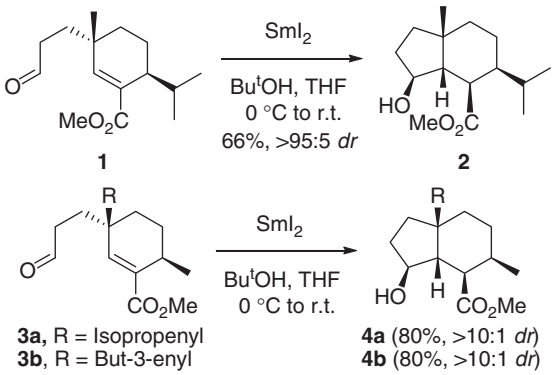
Tin-free radical cyclizations are a subject of tremendous interest in modern organic synthesis.[19] The quest to employ less toxic and more environmentally friendly protocols has stimulated much work in this area. This section covers cyclizations of carbon-centered radicals employing metals other than tin as well as metal-free processes. Many tin-free radical processes can also be found in other sections of this chapter.

4.13.2.1 SmI_2-Mediated Cyclizations and Related Electrochemical Methods

The single-electron reducing agent SmI_2, which was introduced by Kagan in 1977,[26] has been widely used in synthesis. Capable of mediating both radical and polar processes, its utility in radical reactions is primarily due to its ability to generate ketyl radicals from carbonyl-containing functional groups with useful chemoselectivity. Synthetic applications of SmI_2 have been extensively reviewed (*see* Chapter 1.09).[16] This subsection is organized according to the type of radical acceptor, and concludes with related reductive processes that employ electrochemical methods.

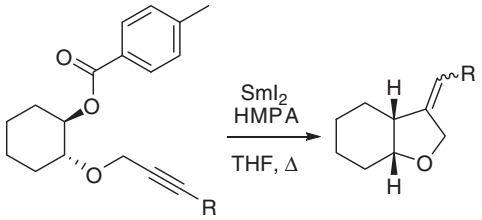
4.13.2.1.1 Alkene acceptors

Cis-fused hydrindanes can be formed in good yield and excellent diastereoselectivity via 5-*exo*-*trig* cyclizations of aldehyde-derived ketyl radicals onto enoate acceptors (Scheme 1).[27] The observed stereochemistry is consistent with cyclization via a chelated antiintermediate followed by protonation of the resulting Sm(III) enolate from the less-hindered α-face.



Scheme 1

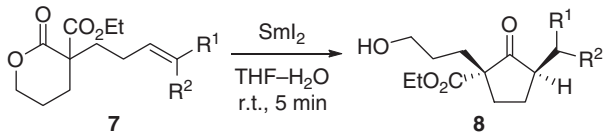
On treatment with SmI_2 and hexamethylphosphoramide (HMPA), toluates **5** undergo reduction and subsequent fragmentation to generate alkyl radicals, which cyclize rapidly to afford tetrahydrofurans (THFs) **6** (Scheme 2).[28] The same reaction can also be performed using electrolysis instead of SmI_2.[29]



Scheme 2

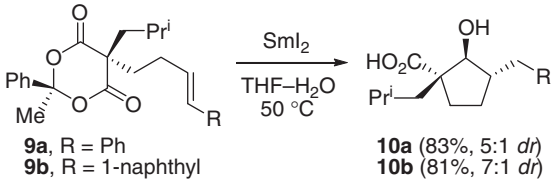
An example of the exquisite chemoselectivity provided by SmI_2 was reported by Procter and coworkers, who demonstrated that six-membered lactones are preferentially reduced by SmI_2–H_2O in the presence of aliphatic esters. The radical anions formed by this method function as acyl radical equivalents in 5-*exo-trig* cyclizations (Table 1).[30] The high diastereoselectivity is attributed to cyclization via an electronically preferred *anti*-transition state with an equatorial radical, and the resulting chelated hemiketal adduct is apparently stable under the reaction conditions, thereby preventing further reduction to give cyclopentanols.

Table 1 Selective single-electron reduction of lactones



Entry	*R^1*	*R^2*	*Yield (%)*	*dr*
1	H	H	56	9:1
2	Me	Me	40	33:1
3	Ph	H	60	12:1
4	Ph	Ph	72	>95:5
5	*p*-MeOPh	H	79	7:1
6	*p*-BrPh	H	73	8:1

Procter and coworkers also demonstrated that cyclic 1,3-diesters can be reduced by SmI_2–H_2O, and the resulting radicals undergo diastereoselective cyclization (presumably through the intermediacy of an axial radical) to ultimately afford cyclopentanols (Scheme 3).[31] Interestingly, the cyclizations exhibited improved diastereomeric ratios at higher temperatures.

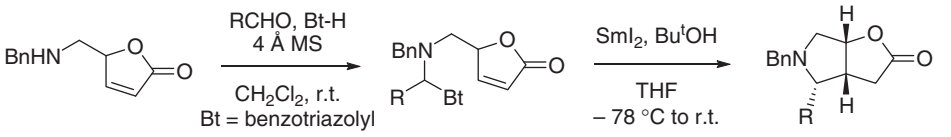


Scheme 3

Adducts generated by condensation of an amine, an aldehyde, and benzotriazole fragment on exposure to SmI_2, producing α-amino radicals. These species can then cyclize onto γ-butenolide acceptors, affording pyrrolofuranones (Scheme 4).[32] The bicyclic products **13a–c** are useful building blocks in organic synthesis.

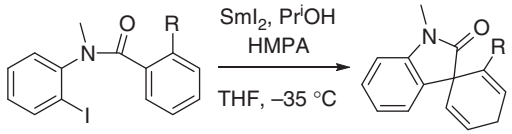
4.13.2.1.2 Aryl and heteroaryl acceptors

Radicals generated by SmI_2 can cyclize onto aromatic and heteroaromatic rings, forming a variety of types of products. Aryl radicals formed from the treatment of *o*-iodobenzamides **14** with SmI_2 and HMPA undergo a 5-*exo* cyclization, delivering spirocycles **15** after subsequent reduction and protonation by Pr^iOH (Scheme 5).[33] The highest yields are obtained with



11 **12a**, R = Pr^n **13a** (71%, 94:6 *dr*)
12b, R = Pr^i **13b** (84%, 83:17 *dr*)
12c, R = $(CH_2)_4CO_2Me$ **13c** (66%, 94:6 *dr*)

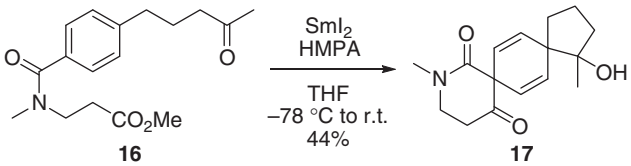
Scheme 4



14a, R = Me **15a** (89%)
14b, R = OMe **15b** (89%)

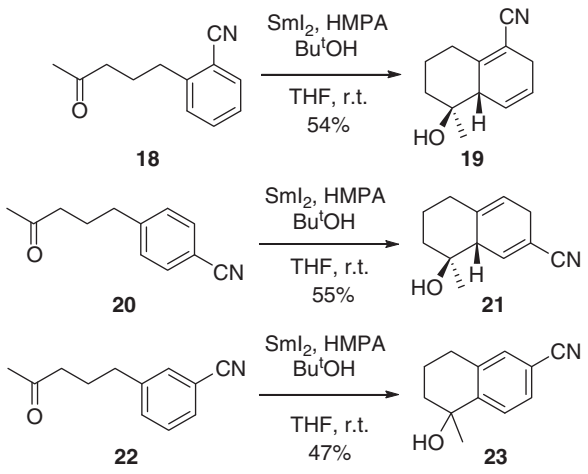
Scheme 5

electron-rich aryl acceptors. Naphthalene and indole rings can also be used as acceptors. A related tandem spirocyclization in which the incipient cyclohexadienyl anion is trapped by a pendant ester has also been developed (equation 1).[34]



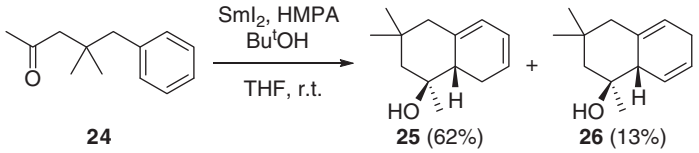
16 **17** (1)

Reissig and coworkers have extensively studied SmI_2-promoted cyclizations of ketyl radicals onto aryl and heteroaryl acceptors. Cyclizations of γ-aryl ketones are favored by the presence of electron-withdrawing groups on the benzene ring (**Scheme 6**).[35] The *o*- and *p*-substitution patterns (e.g., **18** and **20**, respectively) lead to hexahydronaphthalenes, whereas *m*-substrates (e.g., **22**) deliver rearomatized products. The anionic cyclized intermediates derived from **22** and other *m*-substrates can be trapped with electrophiles (i.e., acetone and allyl bromide) to prevent rearomatization. Geminal disubstitution on the alkyl chain promotes cyclization, and in these cases electron-withdrawing groups are not required for good yields (equation 2).[36] However, a mixture of isomers favoring the conjugated diene is obtained.



18 **19**
20 **21**
22 **23**

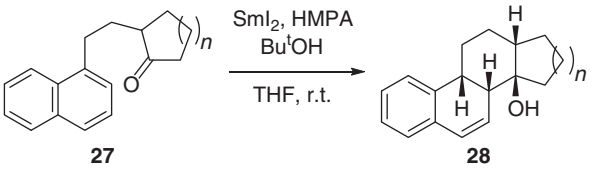
Scheme 6



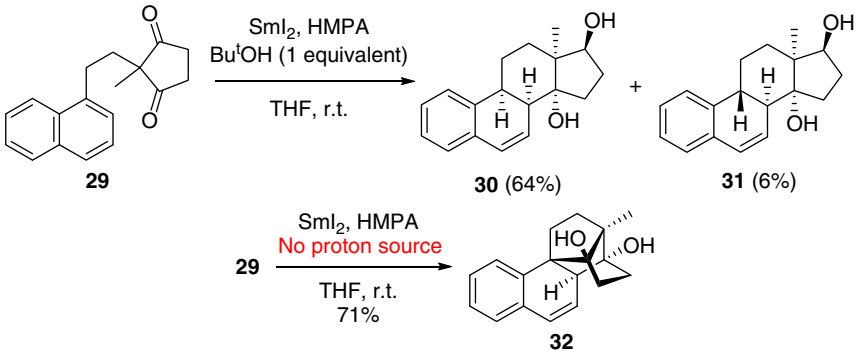
24 **25** (62%) + **26** (13%) (2)

γ-Naphthyl-substituted 4–8-membered cyclic ketones **27** undergo SmI_2-promoted cyclization to afford steroid-like tetracycles **28** possessing an unnatural *cis–cis* fusion (Table 2).[37] Incorporation of a nitrogen atom into the cycloalkanone moiety furnishes azasteroid derivatives.[37b] Cyclic 1,3-diones can also undergo this transformation, but precise control over the equivalents of Bu^tOH is required to ensure high stereoselectivity in the protonation step (Scheme 7).[38] When the reaction of **29** is conducted in the absence of a proton source, a tandem cyclization occurs to provide bridged diol **32**.

Table 2 Steroid-like compounds via SmI_2-mediated cyclizations



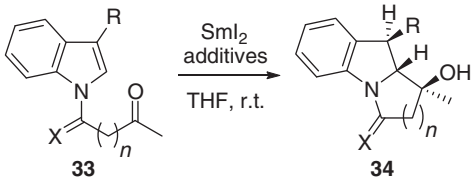
Entry	*n*	*Yield (%)*
1	0	41
2	1	80
3	2	96
4	3	98
5	4	52



Scheme 7

Indoles are versatile acceptors for ketyl radicals, as demonstrated by the SmI_2-mediated cyclizations of substrates **33**. These reactions afford tricyclic adducts **34** as single diastereomers in good yields (Table 3).[39] The bulky Sm(III) alkoxide is believed to

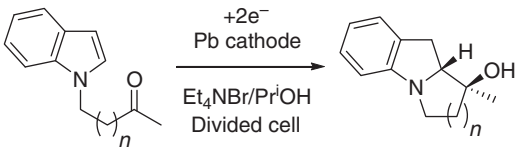
Table 3 Diastereoselective ketyl radical cyclizations onto indole acceptors



Entry	*R*	*X*	*n*	*Additives*	*Yield (%)*
1	H	H and H	1	HMPA and phenol	70
2	H	H and H	2	HMPA and phenol	73
3	CO_2Me	H and H	1	HMPA and Bu^tOH	90
4	CO_2Me	H and H	2	HMPA and Bu^tOH	85
5	H	O	2	HMPA and phenol	73
6	CO_2Me	O	2	Bu^tOH	97

occupy an equatorial or pseudoequatorial position in the transition state. When two electron-withdrawing groups are attached to the indole system, the use of HMPA is no longer necessary (entry 6). Similar reactions are possible with pyrrole derivatives. Other electron-withdrawing groups (i.e., nitrile and acetonitrile) can be present at the C-3 position of indole substrates.[40] The Sm(III) enolates derived from cyclizations of ester-containing substrates (i.e., entries 3, 4, and 6) can also be trapped with alkyl halides to afford more highly functionalized products.[41]

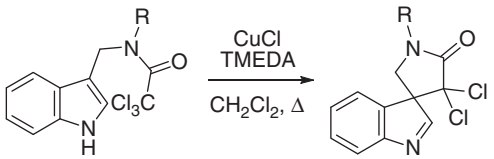
Ketyl radical cyclizations similar to those possible with SmI_2 can be accomplished using electrochemistry. For example, electroreductive cyclizations of indolealkanones **35** proceed in a manner analogous to the SmI_2-promoted transformations shown above (Scheme 8; cf. Table 3, entries 1 and 2).[42] Small amounts (12%) of the reduced, uncyclized alcohol are generated in the cyclization of **35a**. This method is attractive because it avoids use of the expensive reagent SmI_2 and the toxic additive HMPA.



Scheme 8

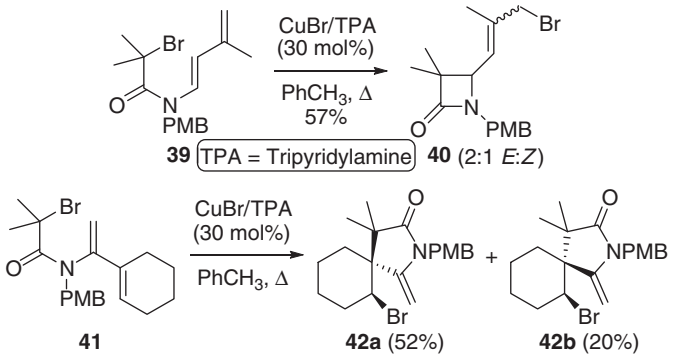
4.13.2.2 Cu-Promoted Atom Transfer Radical Cyclizations

Copper(I) salts have been used extensively to mediate atom transfer cyclizations, with the majority of examples involving reactions of α-polychlorinated amides.[14] Contemporary research in this area has focused on expansion of the substrate scope as well as the development of catalysts that are simple, inexpensive, or environmentally friendly. Spirocyclic imines **38** are formed via the CuCl–tetramethylethylenediamine (TMEDA)-catalyzed cyclization of *N*-(indolylmethyl)trichloroacetamides **37** (Scheme 9).[43] The initially formed α-chloroamines undergo elimination to generate the sensitive indolenines, which can be reduced ($NaBH_3CN$ and HOAc) to afford more robust indolines. Substrates with an electron-withdrawing group attached to the nitrogen (i.e., tosyl) delivered similar spirocyclic products.



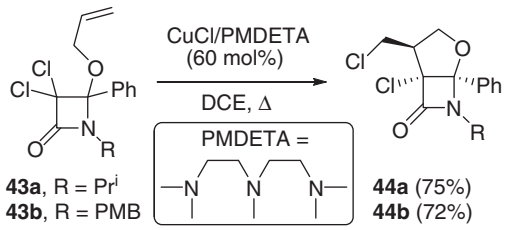
Scheme 9

Cu(I)–tripyridylamine (TPA) catalysts are reactive enough to facilitate atom transfer cyclizations of monobrominated substrates. Reactions of dienamides afford different products depending on the substitution patterns. The 3-substituted dienamides (e.g., **39**) furnish β-lactams, whereas 2-substituted dienamides (e.g., **41**) provide spirocycles via a 5-*exo* process (Scheme 10).[44]



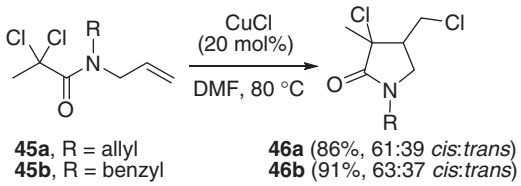
Scheme 10

Fused bicyclic β-lactam derivatives are available by means of 5-*exo* cyclizations of dichlorinated β-lactams **43** (Scheme 11).[45] The chloromethyl group in **44** provides a handle for further functionalization.



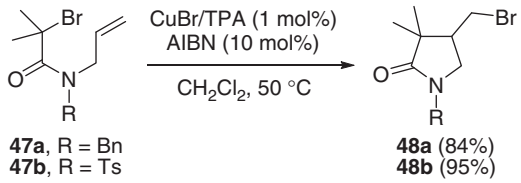
Scheme 11

Most Cu(I)-promoted atom transfer radical cyclizations require polydentate amine ligands. However, when Lewis basic dimethylformamide (DMF) is employed as the solvent in reactions of *N*-allyl dichloroamides **45**, such a ligand is not required (Scheme 12).[46]



Scheme 12

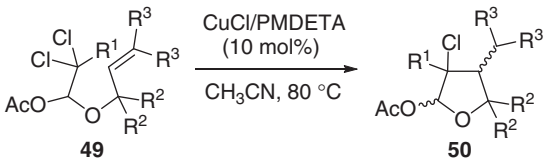
Traditionally, high catalyst loadings (20–60 mol%) have been required for copper-catalyzed atom transfer radical cyclizations. Clark and Wilson[47] have found that azobisisobutyronitrile (AIBN) can function as a reducing agent to prevent the buildup of Cu(II) species, thereby permitting reduced catalyst loadings (Scheme 13). Interestingly, $CuBr_2$ is also a viable catalyst in these reactions. Other practical developments in the formation of lactams by this method include reusable catalysts encapsulated in the polysiloxane gel,[48] and the utilization of ethanol and ascorbic acid as an environmentally friendly solvent and reductant, respectively.[49]



Scheme 13

Highly substituted γ-lactones have been constructed via a two-step process beginning with CuCl/pentamethyldiethylenetriamine (PMDETA)-catalyzed 5-*exo* cyclization of 2,2-dichlorohemiacetal acetates **49** (Table 4).[50] The resulting mixture of four diastereomers converges to give two isomeric lactones (i.e., *cis* and *trans*) after a one-pot hydrolysis–oxidation protocol.

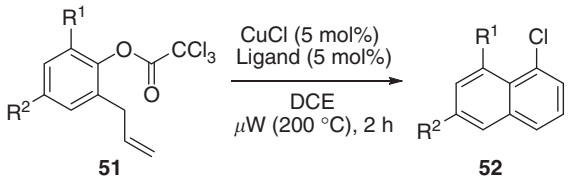
Table 4 Cu-catalyzed cyclizations of 2,2-dichlorohemiacetal acetates



Entry	R^1	R^2	R^3	*Yield (%)*	*dr*
1	Me	H	H	84	13:54:21:12
2	Me	Me	H	91	16:22:36:26
3	Me	H	Me	89	21:42:25:12
4	*i*-Pr	H	H	93	22:48:27:3

Quayle and coworkers have reported an interesting Cu(I)-catalyzed, microwave-promoted benzannulation process (Table 5).[51] The reaction is believed to proceed via initial 8-*endo* atom transfer radical cyclization followed by generation of a second α-carbonyl radical, 4-*exo* cyclization onto the aromatic ring, loss of CO_2, and elimination of HCl (Scheme 14). An imidazolium salt is employed as the ligand, and a preformed Cu(I)–*N*-heterocyclic carbene complex can also be employed as the catalyst.[52]

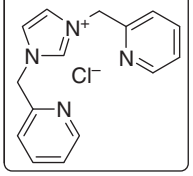
Table 5 Cu(I)-catalyzed benzannulations

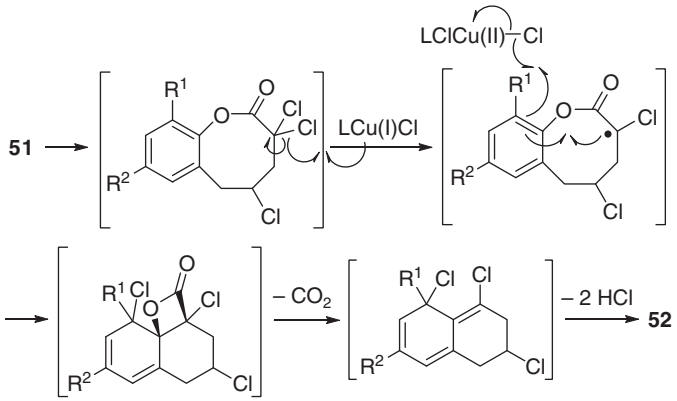


51 52

Entry	R^1	R^2	Yield (%)
1	OMe	H	74
2	Ph	H	78
3	CHO	H	59
4	H	CO_2Me	91
5	H	OMe	67
6	H	OAc	89

Ligand:





Scheme 14

4.13.2.3 Cyclizations Mediated by Ti(III) Reagents

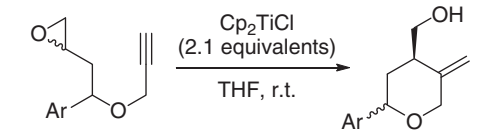
In 1988, Nugent and RajanBabu[53] discovered that Cp_2TiCl reacts with epoxides to furnish β-alkoxy radicals, which can then undergo a variety of transformations. Since then, Ti(III) reagents have played a prominent role in organic synthesis.[13] Cp_2TiCl was first introduced as a stoichiometric reagent, but a growing number of processes are catalytic in Ti.

4.13.2.3.1 Stoichiometric processes

Treatment of epoxyalkyl propargyl ethers **53** bearing electron-neutral or electron-rich aryl groups with Cp_2TiCl induces 6-*exo-dig* cyclization, affording functionalized THFs **54** (Scheme 15).[54] The epoxides can be employed as a 1:1 mixture of diastereomers, and moderate selectivity for the *cis* product is observed in harmony with the Beckwith–Houk model.

When epoxides **55** are exposed to Ti(III), the resulting β-alkoxy radical cyclizes in a 5-*exo-trig* fashion, and the subsequent β-elimination of a phosphinoyl radical affords *exo*-alkylidene pyrrolidines **56** (Scheme 16).[55] In this case, the Ti(III) reagent is generated *in situ* by reduction of Cp_2TiCl_2 with Mn.

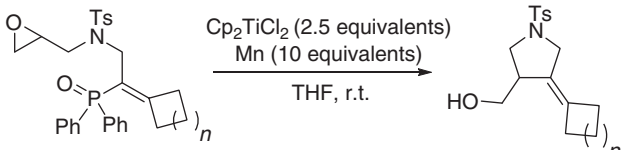
Allenes can be used as acceptors in Ti-promoted radical cyclizations of epoxides (Table 6).[56] The resulting 3-vinyl-4-hydroxymethyl THFs **58** are isolated as diastereomeric mixtures.



53a, Ar = Ph
53b, Ar = *p*-OMePh

54a (78%, 4.6:1 *cis*:*trans*)
54b (72%, 4:1 *cis*:*trans*)

Scheme 15

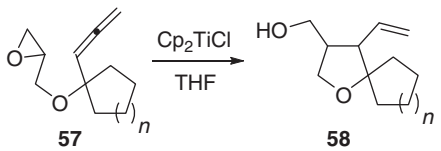


55a, *n* = 1
55b, *n* = 2
55c, *n* = 3

56a (57%)
56b (58%)
56c (82%)

Scheme 16

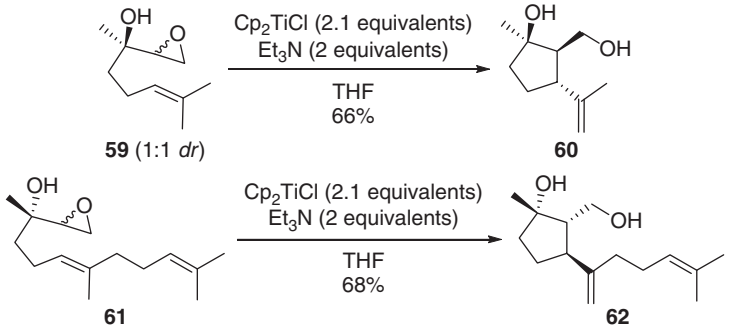
Table 6 Ti-promoted radical cyclizations onto allenes



57 **58**

Entry	*n*	*Yield (%)*	*dr*
1	1	84	64:36
2	2	72	64:36
3	3	76	63:37
4	4	71	62:48

Epoxy alcohols **59** and **61** undergo stereoselective Ti(III)-mediated cyclizations followed by oxidative termination, providing functionalized cyclopentanes **60** and **62** in good yield (Scheme 17).[57] The use of Et_3N is critical to minimizing the amounts of byproducts derived from reductive termination events. The stereoselectivity is presumably due to chelation control.

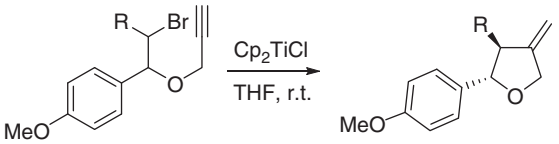


59 (1:1 *dr*) **60**

61 **62**

Scheme 17

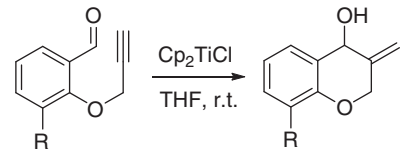
Ti(III) reagents can generate radicals from functional groups other than epoxides. For example, α-bromo ester **63a** and α-bromo ketone **63b** participate in 5-*exo*-*dig* cyclizations on treatment with Cp_2TiCl, delivering THFs **64a** and **64b** (Scheme 18).[58] Additionally, aryl aldehydes **65** react with Cp_2TiCl to form ketyl-type radicals, which cyclize in a 6-*exo* fashion to produce benzopyrans **66** (Scheme 19).[59]



63a, R = CO_2Me
63b, R = COMe

64a (85%)
64b (70%)

Scheme 18



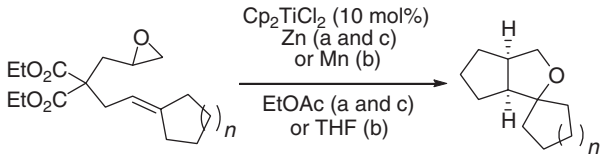
65a, R = H
65b, R = OMe

66a (75%)
66b (70%)

Scheme 19

4.13.2.3.2 Catalytic processes

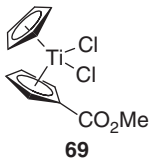
Reactions that utilize catalytic amounts of Ti(III) typically require a weak acid to protonate the Ti-bound oxygen atom and allow catalyst turnover. Gansäuer and coworkers have demonstrated that 2,4,6-collidine hydrochloride (Coll · HCl) could be used for this purpose.[60] In most cases, the Ti(IV) complex Cp_2TiCl_2 is employed as the catalyst precursor, and the active catalyst is generated by reduction using manganese metal. In reactions of epoxides **67**, Coll · HCl is not required for catalyst turnover, as this occurs via an unusual homolytic substitution at oxygen with cleavage of the Ti–O bond, furnishing bicyclic products **68** (Scheme 20).[61] Replacement of Cp_2TiCl_2 with precatalyst **69** (Figure 1) results in a more efficient catalyst that allows less reactive substrates to participate in this process.[62]



67a, $n = 1$
67b, $n = 2$
67c, $n = 3$

68a (61%)
68b (62%)
68c (62%)

Scheme 20



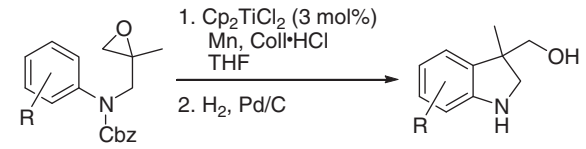
69

Figure 1 Ti(IV) precatalyst.

Aromatic rings are viable acceptors in Ti(III)-catalyzed radical cyclizations. The indoline nucleus, which is prevalent in bioactive natural products, can be constructed via cyclization of *N*-carbobenzyloxy (*N*-Cbz) anilines **70** and subsequent deprotection (Scheme 21).[63] Unprotected anilines are not compatible with the reaction.

The development of new hydrogen atom donors that are inexpensive and nontoxic is of great interest. Gansäuer and coworkers have found that the product of oxidative addition of H_2 to Vaska's complex ($IrCl(CO)(PPh_3)_2$) is a suitable hydrogen atom transfer agent in Ti(III)-catalyzed cyclizations of epoxy alkynes **73** (Scheme 22).[64] As this complex is only present in catalytic amounts, premature reduction of the β-alkoxy radical before cyclization does not occur. Vaska's complex is ideal for this transformation due to its rapid oxidative addition to H_2 and its inability to catalyze alkyne (or alkene) hydrogenation.

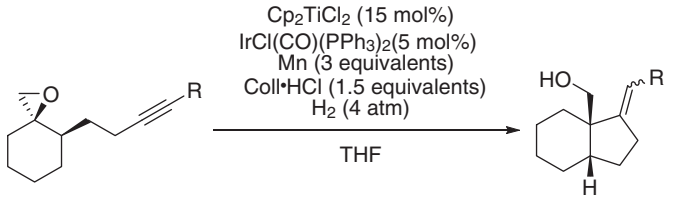
Titanium reagents other than Cp_2TiCl_2 and Cp_2TiCl can play vital roles in radical processes. When an arenediazonium salt (e.g., p-$MeOC_6H_4N_2^+ \cdot {}^-BF_4$) is treated with $TiCl_3$, aryl radicals are formed, and these species are suitable initiators for atom



70a, R = *p*-Me
70b, R = *o*-Me
70c, R = *p*-CO_2Me

71a (62%)
71b (35%)
71c (56%)

Scheme 21



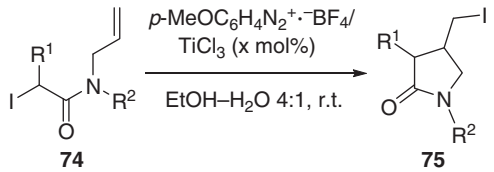
72a, R = CH_3
72b, R = Ph

73a (88%, 63:37 *dr*)
73b (68%, 85:15 *dr*)

Scheme 22

transfer radical cyclizations (Table 7).[65] Ditin reagents are often used in these reactions, and the development of alternative initiators is desirable. Only 5–10 mol% of the initiating system is required to produce high yields of the products.

Table 7 Ti(III)-catalyzed atom transfer radical cyclizations



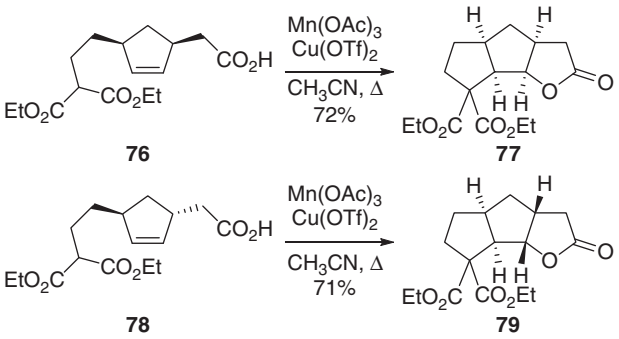
74 **75**

Entry	R^1	R^2	*x*	*Yield (%)*	*trans:cis*
1	H	Allyl	5	99	–
2	H	Ts	10	96	–
3	Me	Allyl	5	96	78:22
4	Me	Ts	10	91	84:16

4.13.2.4 $Mn(OAc)_3$-Mediated Cyclizations and Related Oxidative Radical Processes

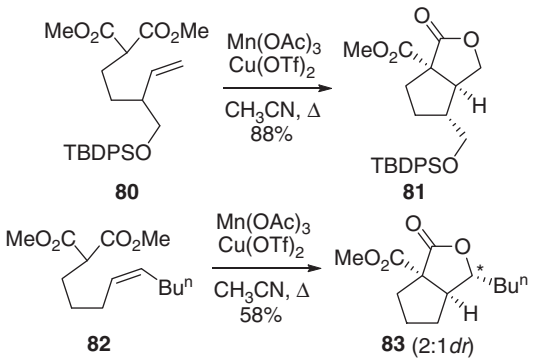
Seminal studies by Snider and coworkers established $Mn(OAc)_3$ as the premier agent for facilitating oxidative radical cyclizations, primarily of 1,3-dicarbonyl compounds.[66] Recent work by others has expanded the scope and utility of $Mn(OAc)_3$-mediated radical processes. Alternative reagents capable of promoting oxidative radical cyclizations have also been introduced. The use of Cu(II) salts in conjunction with $Mn(OAc)_3$ permits a second oxidative process to be coupled to the initial Mn-mediated cyclization. For example, malonates **76** and **78** engage in 5-*exo* cyclizations on exposure to $Mn(OAc)_3$, and the resulting bicyclic radicals participate in Cu(II)-promoted oxidative C–O bond formation, delivering tricyclic lactones **77** and **79** (Scheme 23).[67] Bicyclic lactones **81** and **83** are formed from substrates **80** and **82** in a similar fashion (Scheme 24).[68]

The 6-*endo* cyclization of complex *β*-keto ester **84** is highly dependent on the polarity of the solvent (equation 3).[69] Use of either less polar (i.e., MeOH) or more polar (i.e., pure HOAc) solvents afforded significantly lower yields of adduct **85**. This compound closely matches the left-hand subunit of the natural product hexacyclinic acid.



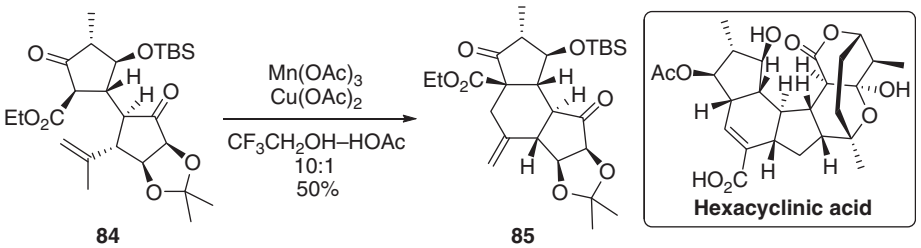
76 **77** **78** **79**

Scheme 23



80 **81** **82** **83** (2:1 *dr*)

Scheme 24



84 **85** (3)

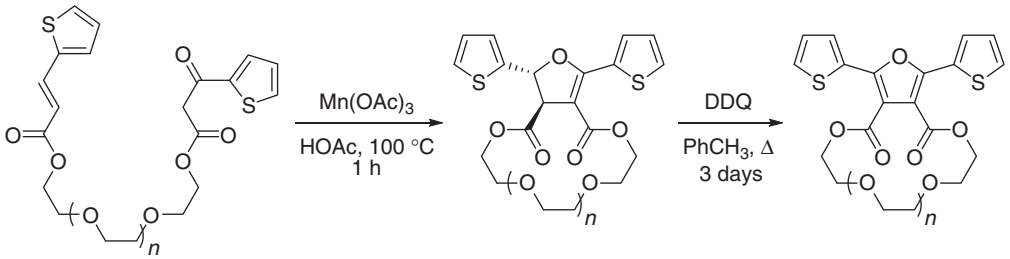
A novel series of 11–23-membered crown ethers **87** can be constructed by means of a facile $Mn(OAc)_3$-mediated macrocyclization (Table 8).[70] Subsequent oxidation affords thiophene/furan oligomers **88**. High-dilution conditions are not required to achieve good yields. It is thought that complexation of the Mn atom by the polyether chain may preorganize substrates **86** in conformations that are favorable for cyclization.

Aromatic rings can function as acceptors in $Mn(OAc)_3$-promoted radical cyclizations. The yields of dihydroquinolinones **90** are high regardless of the electronic nature of the aryl substituent in substrates **89** (Scheme 25).[71] Heteroaromatic systems are also viable acceptors, as evidenced by the cyclizations of indoles **91** (Table 9).[72] Indolo[1,2-*a*]quinolines **93** are obtained on decarboxylation and oxidation of the cyclized products **92**.

Indoles and pyrroles are both effective substrates for Mn(III)-mediated oxidative radical cyclizations (Scheme 26).[73] Interestingly, indolines can also participate in this reaction when subjected to increased loadings of $Mn(OAc)_3$ (Scheme 27), with indole formation and radical cyclization occurring in a one-pot process.[73] The substrate synthesis is higher-yielding with indolines than with indoles or pyrroles, rendering the latter method advantageous.

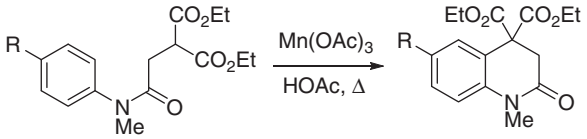
In the course of studies directed toward the welwitindolinone alkaloids, Rawal and coworkers developed a method of controlling the regioselectivity of oxidative radical cyclizations of C3-substituted indoles. Substrate **100** cyclizes onto the C2-position exclusively, affording bridged tetracycle **101** (Scheme 28).[74] However, the chloride substituent at C2 of indole **102** directs the cyclization to C4, delivering tetracycle **103** instead. In addition to serving as a blocking group, the C2 chloride also provides a handle for installation of the oxindole system characteristic of the welwitindolinones.

Table 8 $Mn(OAc)_3$-promoted macrocyclizations



86 **87** **88**

Entry	*n*	*Yield of **87** (%)*	*Yield of **88** (%)*
1	0	78	83
2	1	67	71
3	2	67	68
4	3	53	90
5	4	72	78

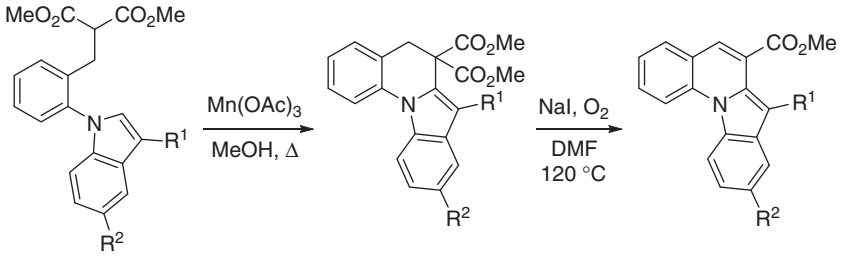


89a, R = H
89b, R = OMe
89c, R = Cl

90a (97%)
90b (97%)
90c (88%)

Scheme 25

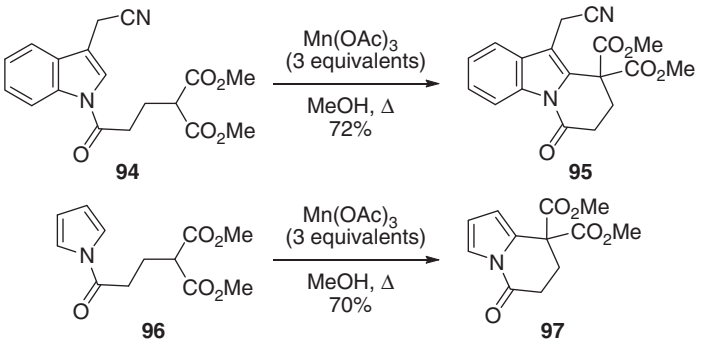
Table 9 $Mn(OAc)_3$-mediated cyclizations onto indole acceptors



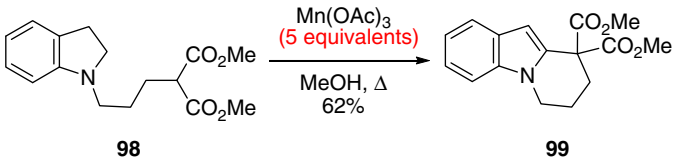
91 **92** **93**

Entry	*R^1*	*R^2*	*Yield of **92** (%)*	*Yield of **93** (%)*
1	H	H	75	70
2	Me	H	77	64
3	H	OMe	78	68

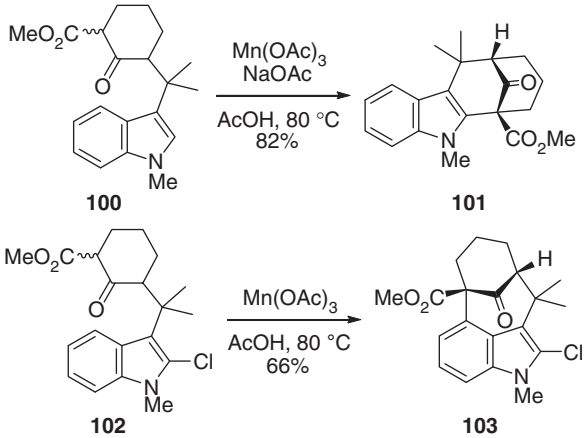
Reagents other than $Mn(OAc)_3$ are capable of promoting oxidative radical cyclizations. Addition of the lithium alkoxide of allyl alcohol to bis-sulfoxide **104** generates an anion that is oxidized on exposure to $(Cp_2Fe)^+ \cdot {}^-BF_4$. The incipient radical undergoes a cyclization–(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) trapping sequence, furnishing THF **105** as a single diastereomer (equation 4).[75] The bis-sulfoxide moiety can subsequently be converted into a ketone or removed to afford a methylene group.



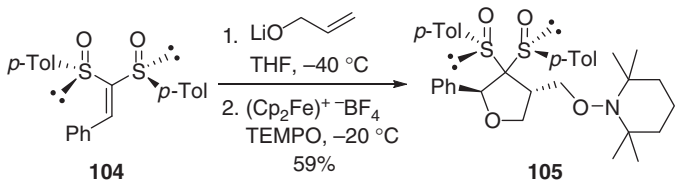
Scheme 26



Scheme 27



Scheme 28

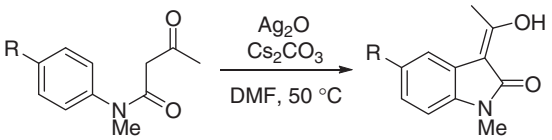


(4)

The combination of Ag_2O and Cs_2CO_3 is useful for mediating cyclizations of acetoacetanilides **106** (Scheme 29).[76] In this case, both $Mn(OAc)_3$ and ceric ammonium nitrate (CAN) were ineffective oxidants.

4.13.2.5 Other Metal-Promoted Cyclizations

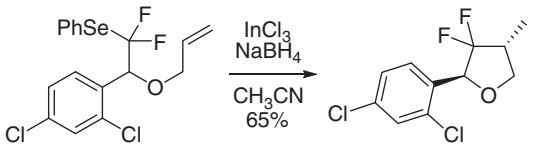
Several metals other than tin and those described above are effective for promoting radical cyclizations. In 2002, Baba and coworkers introduced $InCl_3$–$NaBH_4$ as an alternative for Bu_3SnH in reductive radical cyclizations.[77] Since then, further developments have established the utility of indium reagents in radical chemistry. For example, *gem*-difluorinated THFs have been constructed using the *trans*-selective $InCl_3$–$NaBH_4$-mediated cyclization of phenylselenides (equation 5).[78]



106a, R = H
106b, R = OEt

107a (63%)
107b (57%)

Scheme 29

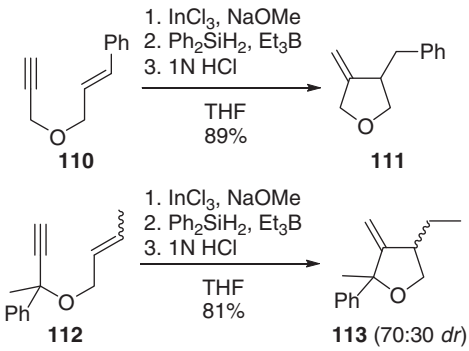


108

109 (16:1 *trans*:*cis*)

(5)

One of the drawbacks of the $InCl_3$–$NaBH_4$ system is the strong reducing ability of the BH_3 byproduct that is generated. This problem can be overcome by reacting Cl_2InOMe, which is generated *in situ*, with Ph_2SiH_2 in the presence of Et_3B. The resulting indium hydride species facilitates the 5-*exo* cyclization of enynes (Scheme 30), and no problematic byproducts are generated.[79] This reagent system can also be applied to cyclizations of 1,2,7-trienes (i.e., allenenes, Table 10).[80]



110

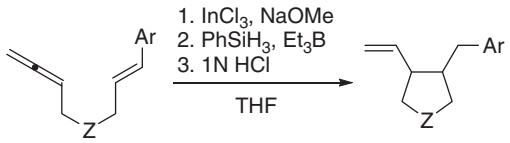
111

112

113 (70:30 *dr*)

Scheme 30

Table 10 Allenes as radical precursors for in-catalyzed cyclizations



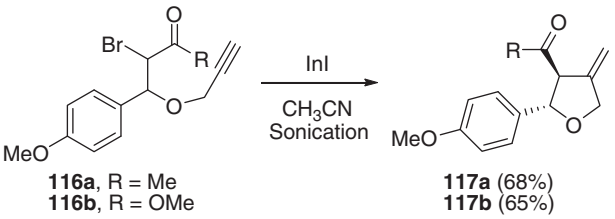
114

115

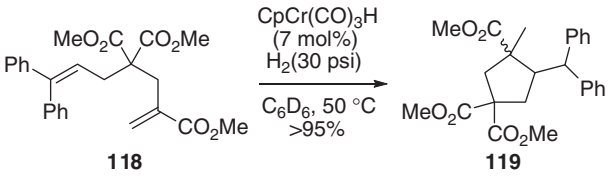
Entry	*Z*	*Ar*	*Yield (%)*	*dr*
1	$C(CO_2Et)_2$	Ph	81	56:44
2	O	Ph	99	87:13
3	O	*p*-ClPh	99	83:17

Indium(I) iodide is capable of promoting the radical cyclizations of α-bromo carbonyl compounds **116** (Scheme 31).[81] Sonication was required for the reaction to proceed, as was the presence of a carbonyl group to stabilize the radical formed after abstraction of the Br atom by InI.

Norton and coworkers discovered that the complex $CpCr(CO)_3H$ can function as a hydrogen atom donor in the radical cyclization of diene **118** (equation 6).[82] This species is regenerated from the corresponding chromium radical on treatment with H_2, allowing its use in substiochiometric quantities. Vanadium hydrides (e.g., $HV(CO)_4(dppe)$) are also effective hydrogen atom donors in this reaction, but two equivalents of the reagent are required as H_2 does not regenerate the metal hydride in this case.[83]

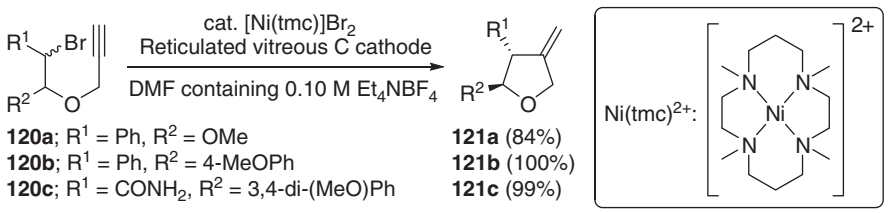


Scheme 31

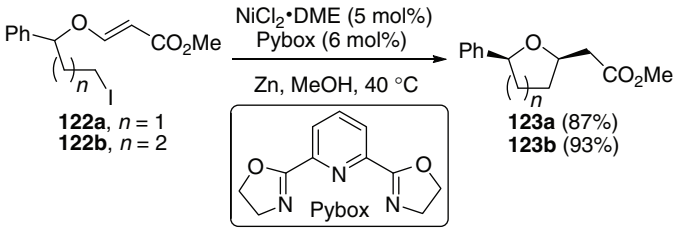


(6)

Some nickel complexes are useful catalysts for reductive radical cyclizations. An Ni(I) tetramethylcyclam catalyst, which is regenerated by electrolysis, can facilitate the 5-*exo-dig* cyclizations of bromo propargyl ethers **120**, delivering *trans*-substituted methylenetetrahydrofurans **121** stereoselectively (Scheme 32).[84] The species formed by reduction of the $NiCl_2 \cdot$1,2-dimethoxyethane (DME)/Pybox complex with Zn catalyzes the 5- and 6-*exo* cyclizations of *β*-alkoxy acrylates **122**, affording cyclic ethers **123** as single diastereomers (Scheme 33).[85] Azacycles and carbocycles are also accessible by this method.



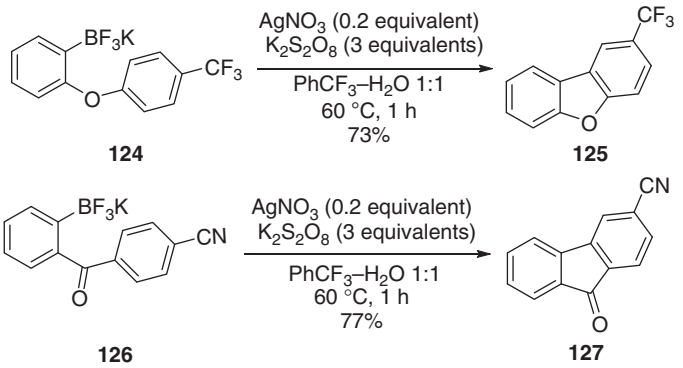
Scheme 32



Scheme 33

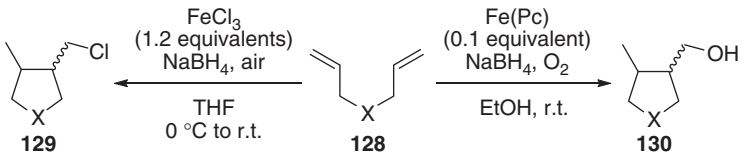
Baran and coworkers have reported that aryl trifluoroborates can serve as radical precursors and participate in Ag-catalyzed cyclizations onto aromatic rings (Scheme 34).[86] This method provides a convenient alternative to the Pschorr reaction, which employs arenediazonium salts as the aryl radical precursors. A useful variant involves aryl radical cyclization onto an alkene followed by trapping of the resultant radical with 1,4-benzoquinone.[86]

Ishibashi and coworkers have investigated iron-promoted radical cyclizations of dienes. Treatment of dienes **128** with stoichiometric $FeCl_3$ and $NaBH_4$ in air results in 5-*exo-trig* cyclization and chlorination of the resulting radical (Table 11). Alternatively, use of catalytic iron phthalocyanine (Fe(Pc)) in an oxygen atmosphere delivers alcohols **130** instead of chlorides **129**.[87] In a related process, thermal decomposition of $Fe(NO_3)_3 \cdot 9H_2O$ in the presence of a diene (e.g., **131**) and $FeCl_3$ induces nitro radical addition to an alkene, 5-*exo* cyclization, and chlorination, generating functionalized adducts (e.g., **132**, equation 7).[88]

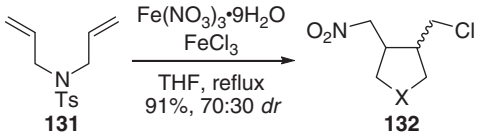


Scheme 34

Table 11 Fe-promoted radical cyclizations of dienes

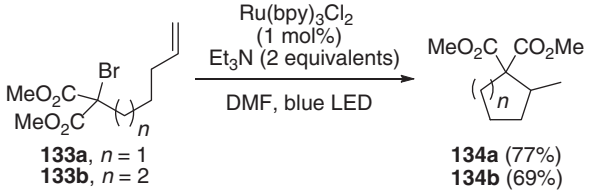


Entry	*X*	***129***		***130***	
		Yield (%)	*dr*	*Yield (%)*	*dr*
1	NTs	69	75:25	63	75:25
2	$C(SO_2Ph)_2$	74	70:30	81	70:30
3	O	76	75:25	61	75:25



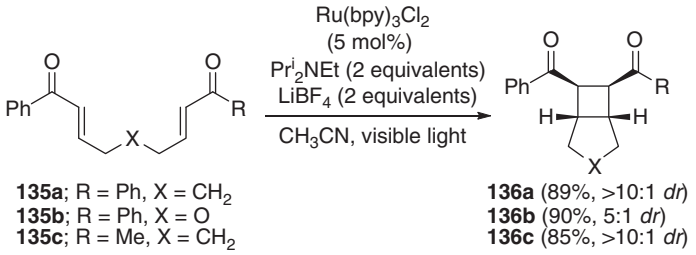
(7)

Visible light photoredox catalysis is a promising area with great potential to render organic synthesis more convenient and environmentally friendly.[89] The combination of a photoactive transition metal catalyst (e.g., $Ru(bpy)_3Cl_2$), a reductive quencher (e.g., a trialkylamine), and a simple light source allow tin-free reductive radical cyclizations to proceed. Stephenson and coworkers discovered that activated alkyl bromides **133** undergo cyclization on treatment with $Ru(bpy)_3Cl_2$ and Et_3N under blue light-emitting diode (LED) irradiation, delivering carbocycles **134** (Scheme 35).[90] The tertiary amine is believed to serve a dual purpose as the reductive quenching agent and the hydrogen atom donor. Less activated alkyl halides can also participate in this transformation if a more reactive Ir photoredox catalyst is employed.[90]



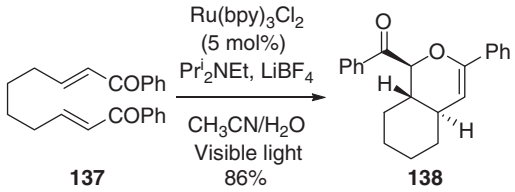
Scheme 35

Yoon and coworkers have studied the photocatalyzed [2 + 2] cycloadditions of enones **135** (Scheme 36).[91] On complexation with Li^+, an aryl enone is reduced to the corresponding radical anion, which participates in a cycloaddition with the pendant enone. Aliphatic enones are not reduced by the photocatalyst, but a compound containing a single aryl enone (i.e., **135c**) is a

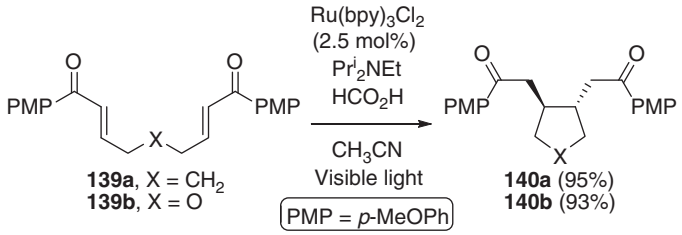


Scheme 36

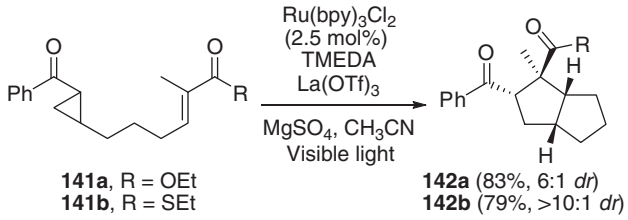
viable substrate. Increasing the tether length between the enones causes a radical anion hetero-Diels–Alder cycloaddition to occur (equation 8).[92] When a Brønsted acid is used instead of a Lewis acid to activate the enone, a diastereoselective reductive cyclization ensues instead of a [2 + 2] cycloaddition (Scheme 37).[93] If the Ru catalyst is replaced with a more potent Ir catalyst, aliphatic enones are able to participate in this reaction. Subjection of aryl cyclopropyl ketones **141** to the cycloaddition protocol with a stronger Lewis acid ($La(OTf)_3$) and a different reductive quenching agent (TMEDA) enables [3 + 2] cycloadditions to proceed (Scheme 38).[94]



(8)

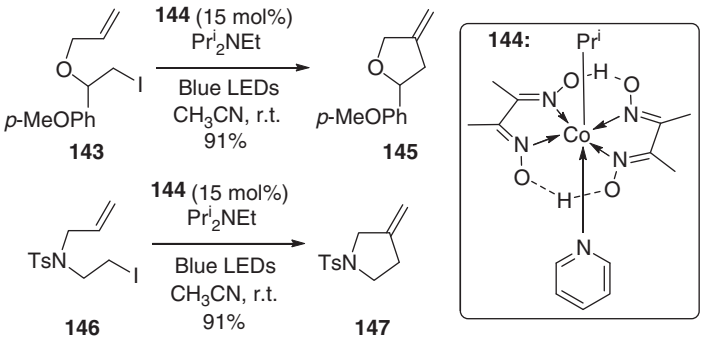


Scheme 37

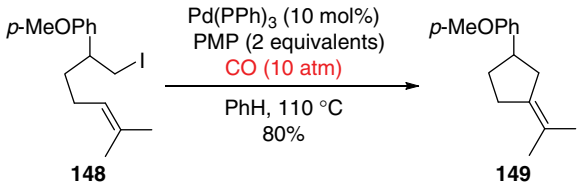


Scheme 38

A cobalt-catalyzed, light-promoted Heck-type cyclization has been reported by Carreira and coworkers (Scheme 39).[95] Irradiation of cobaloxime complex **144** with blue LEDs in the presence of alkyl halides presumably induces formation of an organocobalt(III) species, which undergoes alkene insertion and β-elimination to produce the desired product. The ability to deprotonate the hydridocobalt(III) species with an amine base is critical to enabling catalyst turnover. A related Heck-type process that is believed to involve single-electron transfer from Pd(0) to alkyl iodide **148** and subsequent radical cyclization was developed by Alexanian and coworkers (equation 9).[96] The fact that ring formation is inhibited by TEMPO provides evidence for a radical pathway. Interestingly, CO facilitates efficient cyclization, yet no carbonylative cyclization products are observed.

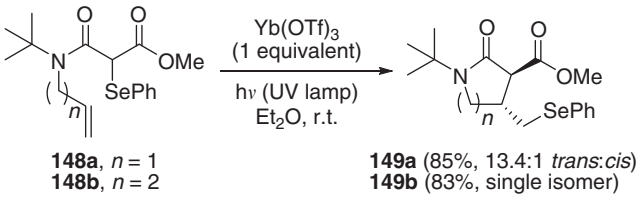


Scheme 39



(9)

Lewis acids can promote radical reactions in a variety of ways.[97] Complexation of Yb(OTf)$_3$ to 1,3-dicarbonyl compounds **148** renders the radicals generated by photolysis of the C–Se bond very electrophilic. Accordingly, 5-*exo* and 6-*exo* cyclizations are accelerated, and group transfer adducts **149** are isolated in high yield (Scheme 40).[98]



Scheme 40

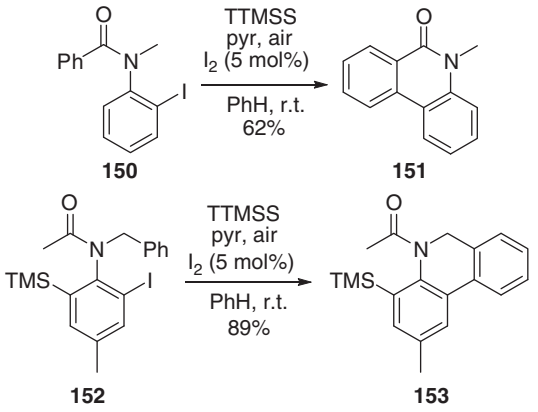
4.13.2.6 Metal-Free Radical Cyclizations

There are several types of metal-free radical cyclizations. Some of these methods employ nonmetal hydrogen atom donors (i.e., substitutes for tin hydrides), whereas others involve nonmetal single-electron transfer agents or electrochemical methods. Additionally, the rich radical chemistry of sulfur has been exploited synthetically in a variety of ways.

4.13.2.6.1 Nonmetal hydrogen atom donors

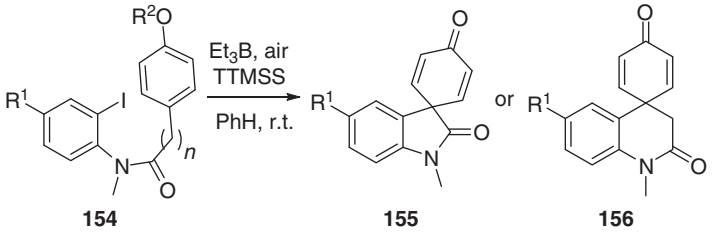
Tris(trimethylsilyl)silane (TTMSS) is a commonly used nonmetal hydrogen atom donor that is larger and slightly less reactive than Bu_3SnH.[18] It is commercially available; alternatively, it can be prepared according to Giese's procedure.[99] Curran and Keller[100] have investigated TTMSS-mediated aryl radical cyclizations onto aromatic acceptors. Aryl iodides **150** and **152** undergo cyclization followed by rearomatization, furnishing biaryls **151** and **153**, respectively (Scheme 41). It is believed that abstraction of a hydrogen atom from the cyclohexadienyl radical intermediate by O_2 causes rearomatization, and the incipient hydroperoxy radical presumably abstracts a hydrogen atom from TTMSS to propagate the chain.

Spirocyclohexadienones **155** and **156** are formed via TTMSS-facilitated *ipso* cyclizations of protected phenols (Table 12).[101] The use of a trityl protecting group favors the required β-fragmentation step, and the other protecting groups (e.g., *tert*-butyldimethylsilyl (TBS) and Me) result in increasing amounts of rearomatized *ortho* cyclization products (cf. Scheme 41). However, a TBS group can be employed in some cases (see entry 3). Replacement of the protected phenol moiety in substrates **154** with an azide also affords spirocyclohexadienones after acidic hydrolysis of the intermediate imines.[102]



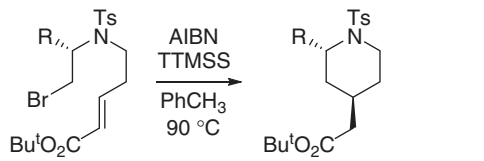
Scheme 41

Table 12 *Ipso* cyclizations of aryl radicals onto protected phenols



Entry	*n*	R^1	R^2	*Product*	*Yield (%)*
1	0	Me	Tr	**155**	53
2	1	H	Tr	**156a**	65
3	1	Me	TBS	**156b**	53

The diastereoselective 6-*exo* cyclizations of substrates **157** (Scheme 42) illustrate one of the key differences between TTMSS and Bu_3SnH. The reaction is significantly more stereoselective with the former reagent (5–6:1 *dr* with Bu_3SnH), and investigations have revealed that the minor *cis* isomer is selectively consumed in a rearrangement of the cyclic piperidine radical involving 1,5-radical translocation and Smiles-type rearrangement. Slower trapping of the cyclic radical with TTMSS than with Bu_3SnH allows this unusual selectivity-enhancing process to occur.[103]



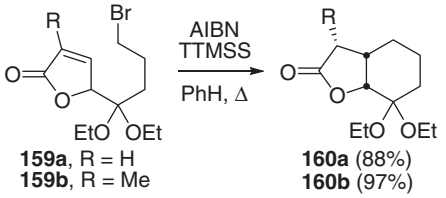
157a, R = Bn
157b, R = Pr^i

158a (62%, 96:4 *trans*:*cis*)
158b (75%, 99:1 *trans*:*cis*)

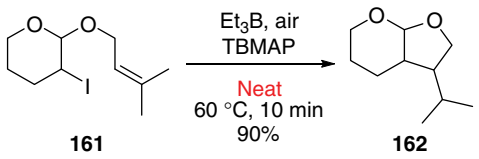
Scheme 42

Bicyclic lactones **160** are synthesized via 6-*exo* cyclizations of substrates **159** with TTMSS as the hydrogen atom donor (Scheme 43).[104] Analogous 4-*exo* cyclizations are also possible. It is believed that the ketal accelerates the reaction due to a Thorpe–Ingold effect. This group also provides a handle for functionalization of the products.

Salts of hypophosphorous acid were introduced by Barton as more environmentally friendly alternatives to Bu_3SnH in radical reactions.[105] A green protocol utilizing tributyl methyl ammonium hypophosphite (TBMAP) as hydrogen atom donor has been developed for the cyclization of haloacetal **161** (equation 10).[106] The reaction proceeds under essentially solvent-free conditions, with only small amounts of hexane used to deliver the Et_3B initiator to the reaction mixture.



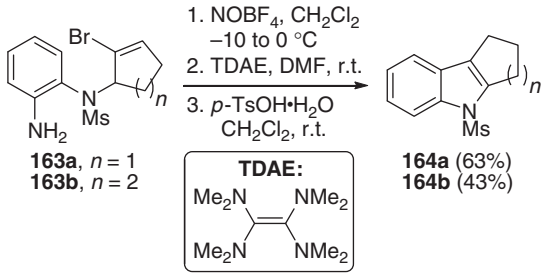
Scheme 43



(10)

4.13.2.6.2 Nonmetal single-electron transfer agents and electrochemical methods

Murphy and coworkers have developed various aza- and thia-substituted neutral organic electron donors. One of these agents, tetrakis(dimethylamino)ethylene (TDAE), is able to reduce arenediazonium salts via single-electron transfer. The resulting aryl radicals follow a 5-*exo* cyclization–elimination pathway, affording fused indoles **164** after acid-promoted alkene isomerization (Scheme 44).[107] TDAE is unable to reduce aryl halides, but the more potent agent **165** (Figure 2) can mediate radical cyclizations of these convenient substrates.[108]



Scheme 44

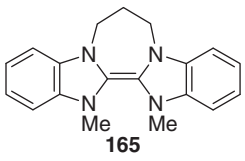
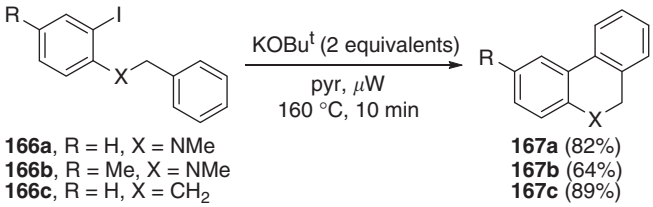


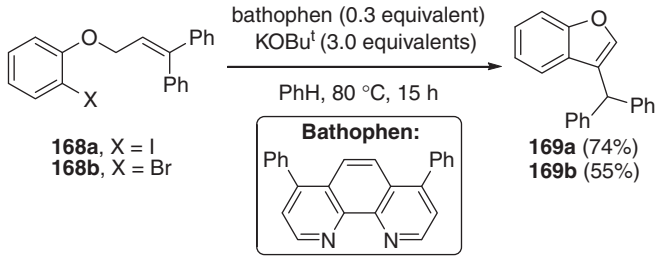
Figure 2 A more potent electron donor than TDAE.

KOBu^t has been shown to generate aryl radicals from aryl halides at high temperatures via a single-electron transfer process. These radicals can participate in cyclizations. In most but not all cases, the presence of a phenanthroline-type ligand accelerates the reaction. Charette and coworkers have described the KOBu^t-promoted cyclizations of aryl halides **166** in the absence of ligands (Scheme 45).[109] Mechanistic experiments support a radical pathway and argue against the existence of a benzyne

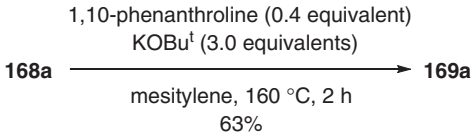


Scheme 45

intermediate. Aryl bromides are also viable radical precursors, provided a phenanthroline ligand is included in the reaction mixture. A related process with neocuproine as the ligand has been published by Shi and coworkers.[110] Recently, two contemporaneous reports of benzofuran synthesis via a KOBu^t-mediated Heck-type cyclization/isomerization process from the groups of Shi (Scheme 46)[111] and Rueping (equation 11)[112] have appeared. Both of these reactions are proposed to involve a radical cyclization step.

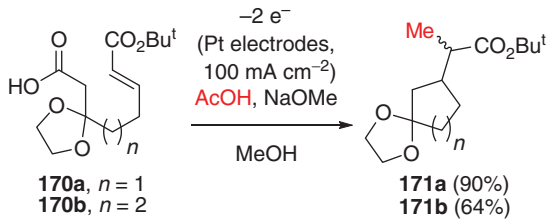


Scheme 46



(11)

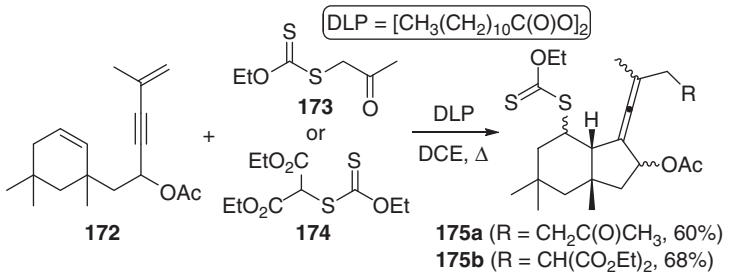
Markó and coworkers have employed the Kolbe oxidative electrolysis to generate alkyl radicals from carboxylic acids **170** (Scheme 47). These species cyclize onto electron-deficient alkenes, and the resulting cyclic radicals are captured by radicals derived from electrolysis of a second acid (e.g., AcOH).[113] Cyclic ethers can also be formed by this method.



Scheme 47

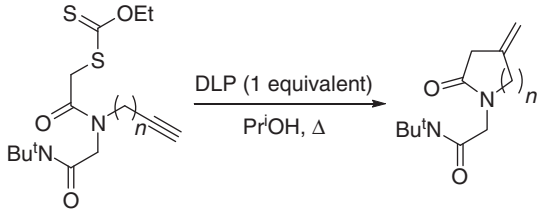
4.13.2.6.3 Cyclizations mediated by sulfur radicals

Sulfur-containing compounds play vital roles in a variety of radical processes.[12] In particular, Zard and coworkers have extensively investigated the use of xanthates in metal-free radical reactions including cyclizations.[114] Treatment of isophorol-derived enyne **172** with xanthates **173** or **174** in the presence of dilauroyl peroxide (DLP) causes intermolecular addition followed by isomerization of the initially formed propargyl radical to an allenyl radical. This species then cyclizes in a 5-*exo* fashion, and the bicyclic radical is trapped with another equivalent of the xanthate to propagate the radical chain and furnish allenes **175a** or **175b** (Scheme 48).[115]



Scheme 48

Under standard xanthate group transfer cyclization conditions (i.e., catalytic DLP and DCE), alkyne substrates **176** do not cyclize cleanly, perhaps due to instability of the putative vinyl xanthate adducts. Fortunately, use of stoichiometric DLP with Pr^iOH as solvent delivers lactams **177** by means of a nonchain process (Scheme 49).[116] Presumably, isopropanol donates a hydrogen atom to the cyclic vinyl radical, preventing formation of a vinyl xanthate.

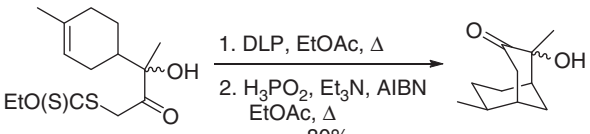


176a, $n = 1$
176b, $n = 2$

177a (68%)
177b (68%)

Scheme 49

Bridged bicyclic compounds can be produced by 6-*exo* xanthate group transfer cyclizations of substrates such as **178** (Scheme 50).[117] Excellent selectivity is observed in the creation of both new stereocenters, and the bicyclic xanthate intermediate can be reduced as shown or subjected to an intermolecular radical addition, giving highly functionalized products.

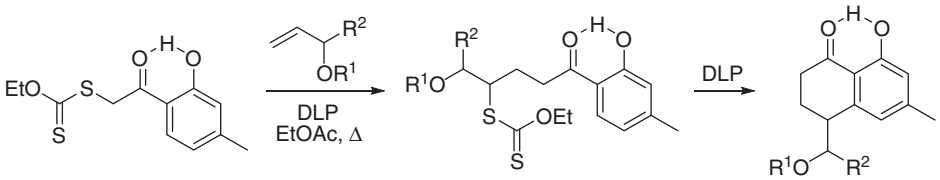


178 (1:1 *dr*)

179 (1:1 *dr*)

Scheme 50

A growing body of work involves cyclization of xanthate-derived radicals onto aromatic and heteroaromatic acceptors. In a two-step process, intermolecular addition of radicals derived from phenol **180** to unactivated terminal alkenes provides xanthates **181**, which then cyclize on exposure to DLP, delivering hydroxytetralones **182** (Scheme 51).[118] A hydrogen bond between the phenol and the neighboring ketone is thought to favor the desired conformation for cyclization, as the ring closure did not occur with the corresponding methyl ether substrate.



180

181a; R^1 = Et, R^2 = OEt (80%)
181b; R^1 = Ac, R^2 = H (85%)

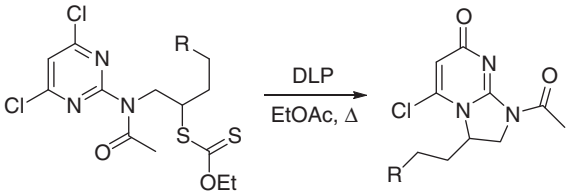
182a (46%)
182b (66%)

Scheme 51

The discovery of an unusual radical cyclization onto a pyridine nitrogen[119] prompted the development of a new synthesis of pyrimidine derivatives. When xanthate-containing dichloropyrimidines **183** are heated in the presence of stoichiometric DLP, pyrimidinones **184** are produced (Scheme 52).[120] Presumably, the intermediate bicyclic radical is oxidized to afford a resonance-stabilized carbocation, which is trapped at the least-hindered site to give a single regioisomeric adduct after workup.

Azaspirocyclic cyclohexadienones **186** are accessible via *ipso* oxidative radical cyclization of xanthates **185** possessing a *p*-methoxy substituent on the aromatic ring (Scheme 53).[121] A conceptually related spirolactamization with furans as the radical acceptors has also been reported.[122] The spirolactamization can be accelerated by microwave irradiation.[123]

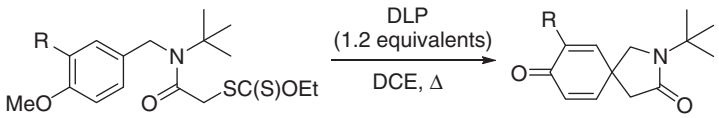
Another example of a sulfur-based radical precursor is the 4-pentynyl sulfide group. Addition of a phenylthiyl radical to the alkyne moiety of substrate **187** generates a vinyl radical, which engages in homolytic substitution at the sulfur atom, forming a cyclic sulfide byproduct and releasing an alkyl radical. This radical subsequently cyclizes to give lactam **188** (equation 12).[124]



183a, R = CN
183b, R = CO_2Me
183c, R = NPhth

184a (80%)
184b (71%)
184c (68%)

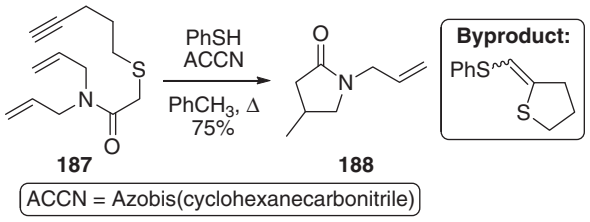
Scheme 52



185a, R = OMe
185b, R = Me
185c, R = Br

186a (75%)
186b (83%)
186c (75%)

Scheme 53



187 **188**

ACCN = Azobis(cyclohexanecarbonitrile)

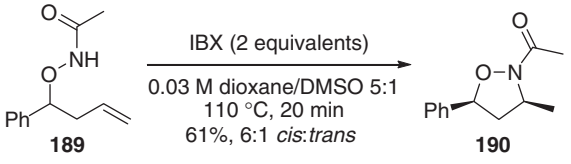
(12)

4.13.3 Cyclizations Involving Heteroatom-Based Radicals or Radical Acceptors

Most radical cyclizations involve carbon-centered radicals and carbon-based acceptors (i.e., alkenes, alkynes, or arenes). However, the use of heteroatom-centered radicals, acyl radicals and related species, or heteroatom-containing acceptors in cyclizations represents an important and emerging field. The products obtained from such reactions are either heterocycles or carbocycles that contain useful functional groups. This section covers each of the types of heteroatom radical cyclizations described above.

4.13.3.1 Nitrogen-Centered Radicals

Several different types of nitrogen-centered radicals have been used in organic synthesis, and this field has been reviewed recently.[10] Alkoxyamidyl radicals can be formed by heating acylated alkoxyamines (e.g., **189**) in the presence of 2-iodoxybenzoic acid (IBX). These radicals cyclize stereoselectively to afford isoxazolidines (equation 13).[125] Byproducts derived from dimerization of the radicals are minimized by conducting the reactions at low concentrations.

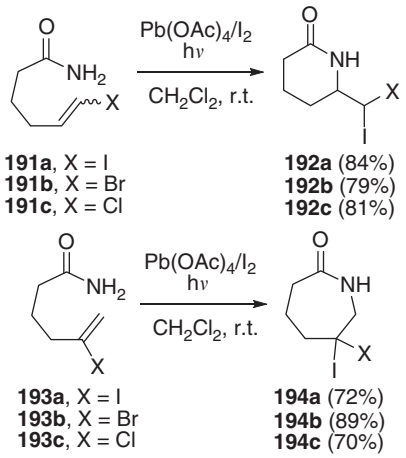


189 **190**

DMSO = dimethylsulfoxide

(13)

The use of vinyl halides as acceptors can have a dramatic impact on amidyl radical cyclizations. A 1,2-substitution pattern causes 6-*exo* cyclization to occur (i.e., **191**→**192**, Scheme 54), whereas 1,1-disubstituted vinyl halides favor a 7-*endo* process (i.e.,**193**→**194**).[126] A lone pair–lone pair repulsion between the amidyl radical and the halogen atom is believed to direct



191a, X = I
191b, X = Br
191c, X = Cl

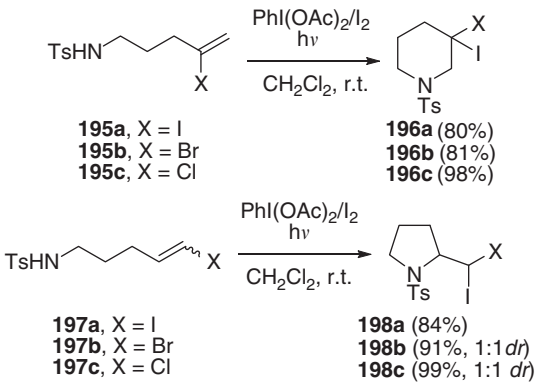
192a (84%)
192b (79%)
192c (81%)

193a, X = I
193b, X = Br
193c, X = Cl

194a (72%)
194b (89%)
194c (70%)

Scheme 54

cyclization to the distal carbon of the acceptor. Similar results are observed in sulfonamidyl (Scheme 55)[127] and carbamidyl radical cyclizations.[128] In the latter reactions, vinylic heteroatoms other than halogens (i.e., O and S) also exert directing effects.



195a, X = I
195b, X = Br
195c, X = Cl

196a (80%)
196b (81%)
196c (98%)

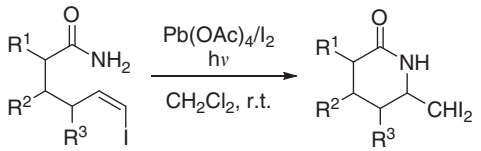
197a, X = I
197b, X = Br
197c, X = Cl

198a (84%)
198b (91%, 1:1 *dr*)
198c (99%, 1:1 *dr*)

Scheme 55

The stereoselectivity of 6-*exo* amidyl radical cyclizations has been investigated. As expected based on chair-like transition states, the 3,6-*trans*, 4,6-*cis*, and 5,6-*trans*-substituted δ-lactams predominate (Table 13).[129] The selectivity is highest with the 5,6-substituted products.

Table 13 6-*exo* amidyl radical cyclizations

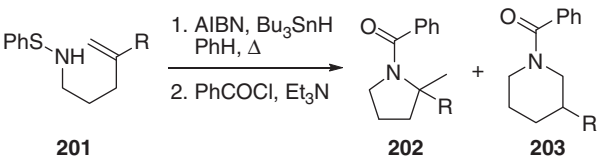


199 **200**

Entry	R^1	R^2	R^3	*Yield (%)*	*trans:cis*
1	Me	H	H	83	75:25
2	H	Me	H	71	11:89
3	H	H	Me	92	95:5

Benzenesulfenamides serve as precursors to aminyl radicals, which are generated on exposure to AIBN and Bu_3SnH. The regioselectivity of aminyl radical cyclizations of substrates **201** can be switched from 5-*exo* to 6-*endo* by increasing the size of the vinylic substituent (Table 14, entries 1–3).[130] A dramatic increase in the preference for the 6-*endo* product is observed with a vinyl chloride acceptor, presumably due to the aforementioned lone pair–lone pair repulsion.

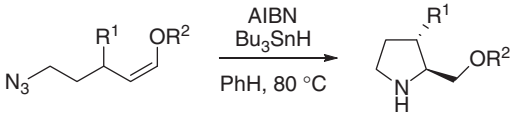
Table 14 Benzenesulfenamides as aminyl radical precursors



201 **202** **203**

Entry	*R*	*Yield of **202** (%)*	*Yield of **203** (%)*
1	H	66	6
2	Me	46	17
3	Bu^t	33	42
4	Cl	4	56

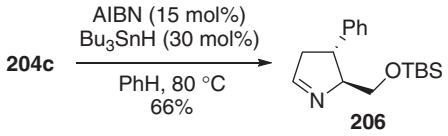
Substituted 2-hydroxymethyl pyrrolidines, which represent a key substructure of polyhydroxylated alkaloids, are accessible via highly stereoselective radical cyclizations of nitrogen-centered radicals derived from azides onto *Z*-silyl enol ethers (Scheme 56).[131] Cyclizations of the corresponding *E*-silyl enol ethers exhibit attenuated stereoselectivity. When the cyclization of azide **204c** is carried out with substoichiometric quantities of Bu_3SnH, imine **206** is produced instead of pyrrolidine **205c** (equation 14).[132] It is believed that an intermolecular hydrogen atom transfer process, which is favored under low concentrations of Bu_3SnH, is responsible for the generation of the imine.



204a, R^1 = OTES, R^2 = TES
204b, R^1 = Me, R^2 = TBS
204c, R^1 = Ph, R^2 = TBS

205a (77%, >95:5 *dr*)
205b (71%, 93:7 *dr*)
205c (68%, >95:5 *dr*)

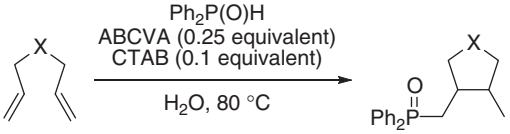
Scheme 56



206 (14)

4.13.3.2 Phosphorus-Centered Radicals

A variety of five-membered carbocycles and heterocycles can be prepared by reactions involving phosphorus-centered radicals. The combination of diphenylphosphine oxide, the water-soluble radical initiator 4, 4′-azobis (4-canovaleric acid) (ABCVA), and the surfactant cetyltrimethylammonium bromide (CTAB) facilitates cyclizations of dienes **207** in water, providing phosphorus-containing adducts **208** in good yield (Scheme 57).[133] When hypophosphorus acid is employed in a related transformation, bispyrrolidine **210** is produced via a sequential radical addition–cyclization reaction (equation 15).[134] An interesting radical addition–translocation–cyclization process occurs on treatment of alkynes **211** with dimethyl phosphite and DLP at high temperatures, furnishing cyclopentanes **212** (Scheme 58).[135] The use of diethyl thiophosphite allows smaller amounts of the phosphorus radical precursor and substoichiometric quantities of the initiator to be employed.[136]

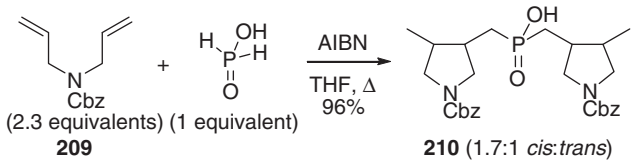


207a, X = O
207b, X = NTs
207c, X = CH_2

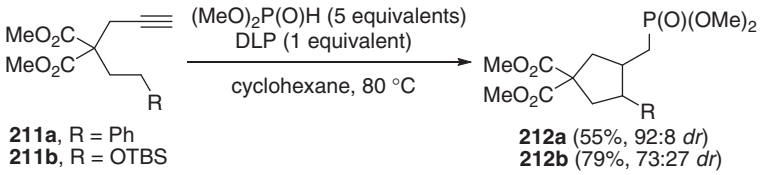
208a (93%, 53:47 *cis*:*trans*)
208b (58%, 63:37 *cis*:*trans*)
208c (74%, 78:22 *cis*:*trans*)

ABCVA = 4,4′-Azobis(4-cyanovaleric acid)
CTAB = Cetyltrimethylammonium bromide

Scheme 57



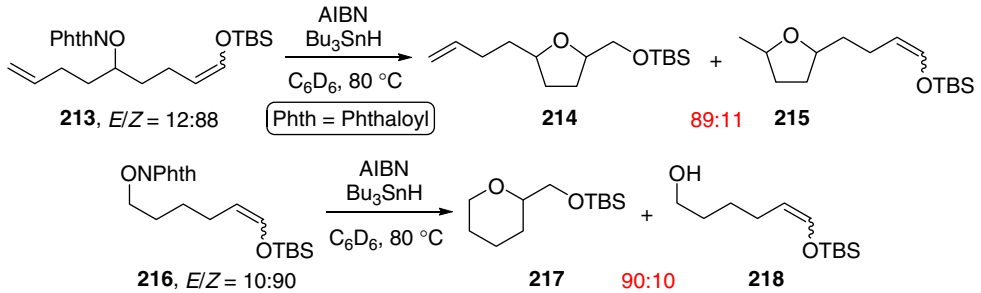
(15)



Scheme 58

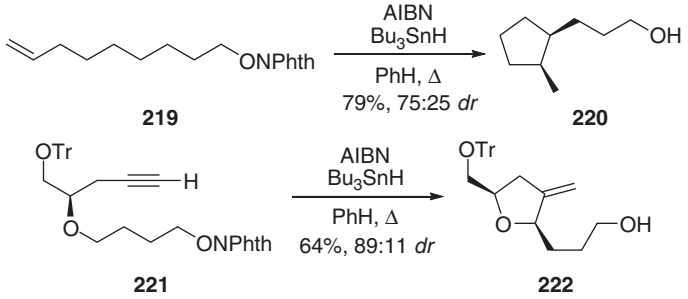
4.13.3.3 Oxygen-Centered Radicals

Cyclizations of oxygen-centered radicals are valuable methods for the construction of THFs and tetrahydropyrans. Hartung and coworkers have conducted extensive mechanistic studies of reactions involving alkoxyl radicals.[11] A recent investigation of 6-*exo-trig* alkenoxyl radical cyclizations has revealed that these processes are irreversible. Thus, the observed stereoselectivities are kinetic in nature, and chair-like transition structures can be used to rationalize the experimental results.[137] The high reactivity of oxygen-centered radicals often causes processes such as 1,5-hydrogen atom transfer and β-fragmentation to compete with cyclization. Sammis and coworkers have discovered that pairing the electron-deficient alkoxy radical with an electron-rich silyl enol ether acceptor can accelerate cyclization, affording cleaner reactions with fewer byproducts. Reactions of substrates **213** and **216** demonstrate that 5-*exo* and 6-*exo* alkoxy radical–silyl enol ether cyclizations are faster than terminal alkene cyclizations and 1,5-hydrogen atom transfers, respectively (Scheme 59).[138]



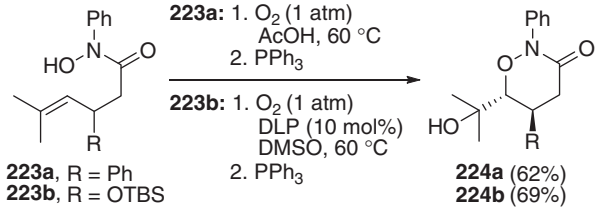
Scheme 59

In a different study, Sammis and coworkers have taken advantage of the propensity of alkoxy radicals to engage in 1,5-hydrogen atom abstractions. Treatment of *N*-alkoxyphthalimide **219** with AIBN and Bu_3SnH sets in motion a radical relay cyclization consisting of alkoxy radical formation, 1,5-hydrogen atom abstraction, and 5-*exo-trig* cyclization, delivering cyclopentane **220** (Scheme 60).[139] This method has a broad scope, tolerating ethers in the tether and alkynes as acceptors (cf. **221** → **222**).

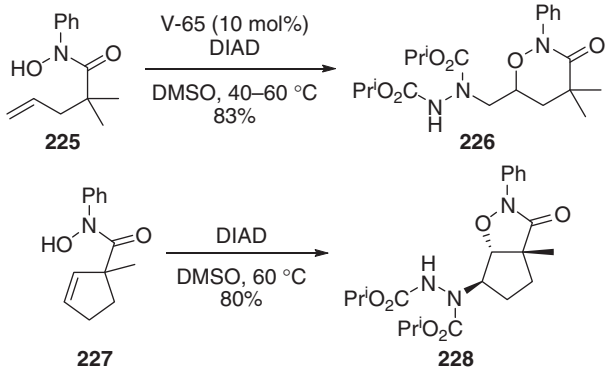


Scheme 60

Schmidt and Alexanian[140] have conducted cyclizations of amidoxyl radicals, which are readily generated from hydroxamic acids. Heating of substrates **223** in the presence of O_2 facilitates a metal-free dioxygenation of the alkene acceptor, delivering adducts **224** stereoselectively after reductive workup with PPh_3 (Scheme 61). Cleavage of the N–O bond is accomplished by treatment with zinc. A related metal-free oxyamination is accomplished with diisopropyl azodicarboxylate (DIAD) as the radical trap (Scheme 62).[141] In this case, selective N–O cleavage is mediated by zinc, whereas simultaneous N–O and N–N cleavage is effected by Raney Ni and ultrasound. The simple reaction conditions, which do not require transition metal catalysts or I(III) oxidants common to other alkene oxidative difunctionalizations, are an attractive feature of these protocols.



Scheme 61

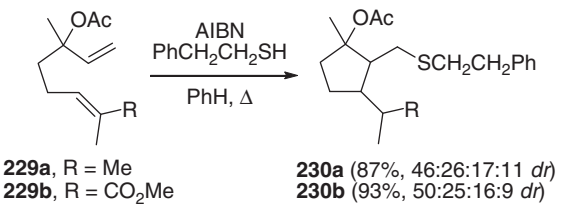


Scheme 62

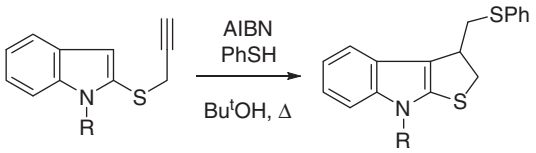
4.13.3.4 Sulfur-Centered Radicals

The additions of sulfur-centered radicals to alkenes or alkynes trigger cyclizations of the resulting alkyl or vinyl radicals, and many different types of interesting and useful products are formed. For example, the iridane monoterpene skeleton is accessible via thiol-promoted 5-*exo-trig* cyclizations of dienes **229** (Scheme 63).[142] Complex mixtures of diastereomers are produced, but stereoconvergent elimination of the acetate group simplifies manipulation of the products.

Thiophenyl radicals add readily to terminal alkynes **231**, and the resulting vinyl radicals cyclize in a 5-*exo* fashion, providing indole-annulated sulfur heterocycles **232** (Scheme 64).[143] The presence of an electron-withdrawing group on the indole nitrogen atom is essential to the success of the reaction. A related thiophenyl radical-triggered vinyl radical cyclization of uracil derivatives furnishes 9-deazaxanthine analogs (equation 16).[144] This process could proceed by either a 4-*exo-trig* cyclization and subsequent neophyl rearrangement or a 5-*endo-trig* cyclization.



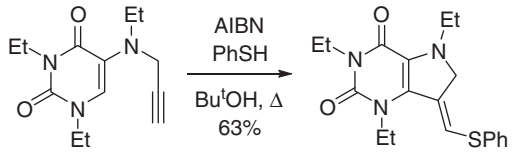
Scheme 63



231a, R = COPh
231b, R = $COCH_3$

232a (68%)
232b (65%)

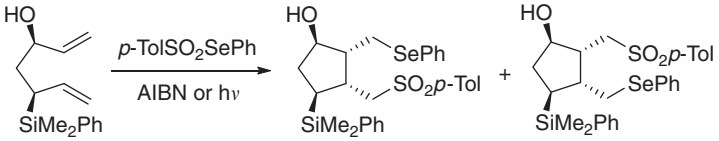
Scheme 64



233 **234** (16)

An allylic silyl group exerts a profound directing effect on the sulfonyl radical mediated 5-*exo* cyclization of diene **235** (Table 15). At low temperatures, addition of the electron-deficient sulfonyl radical to the electron-rich allylsilane is preferred, affording cyclopentane **236** as the major product (entry 1). In contrast, regioisomer **237** is favored at higher temperatures, presumably due to thermodynamic control or a Curtin–Hammett effect (entry 2).[145]

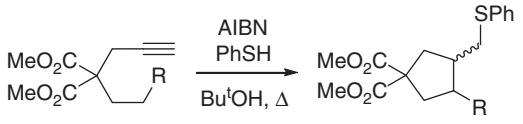
Table 15 Tuning of regioselectivity in 5-*exo* radical cyclizations of dienes



235 **236** **237**

Entry	*Conditions*	*Solvent*	*Temperature (°C)*	***236:237***	*Yield (%)*
1	hν	CH_2Cl_2	−70	90:10	61
2	AIBN	PhH	80	11:89	50

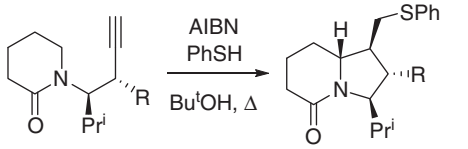
Renaud and coworkers have developed several variants of cyclizations based on the generation of vinyl radicals and subsequent translocation of the radical via 1,5-hydrogen atom transfer.[146] Alkynes **238**, which contain a strategically placed radical stabilizing group, undergo a sequence consisting of thiyl radical addition, 1,5-hydrogen atom transfer, and cyclization, delivering cyclopentanes **239** (Scheme 65).[147] The presence of the phenylthio group in the products provides a convenient handle for further functionalization. Azabicylic compounds are also accessible by this process (Scheme 66).[148]



238a, R = OTBS
238b, R = CO_2Me
238c, R = Ph

239a (89%, 62:38 *dr*)
239b (57%, 76:24 *dr*)
239c (85%, 78:22 *dr*)

Scheme 65

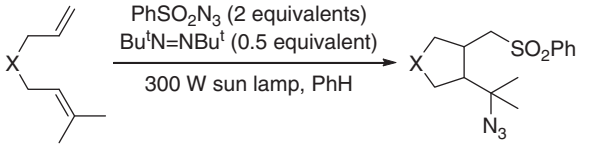


240a, R = Et
240b, R = OMe

241a (87%, 95:5 *dr*)
241b (92%, 78:22 *dr*)

Scheme 66

On photolysis in the presence of di-*tert*-butyldiazene, benzenesulfonyl azide mediates the cyclization of 1,6-dienes **242**, delivering adducts **243** (Scheme 67).[149] Although the diastereomeric ratios are low, the introduction of two functional groups and the creation of one ring render this process useful.



242a, X = $(MeO_2C)_2$
242b, X = NTs
242c, X = O

243a (76%, 2.7:1 *dr*)
243b (89%, 1:1 *dr*)
243c (67%, 1:1 *dr*)

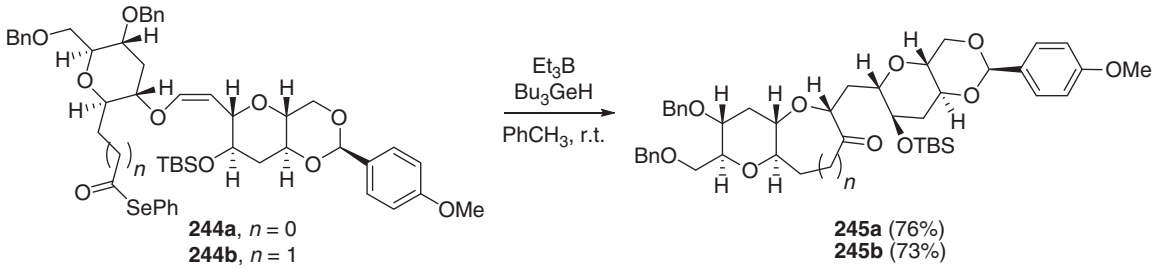
Scheme 67

4.13.3.5 Acyl, Imidoyl, or Iminyl Radicals

Acyl radical cyclizations provide access to a variety of cyclic carbonyl-containing compounds. Recent discoveries have resulted in numerous tin-free methods for acyl radical generation. These species are typically carbon-centered radicals, whereas the nitrogen analogs may exist as either imidoyl (carbon-centered) or iminyl (nitrogen-centered) radicals depending on the nature of the radical precursor.

4.13.3.5.1 Acyl radicals

Polycyclic fused ethers **245** are available via 6-*exo* and 7-*exo* acyl radical cyclizations onto enol ether acceptors (Scheme 68).[150] The use of Bu_3GeH, which is a less reactive hydrogen atom donor than both Bu_3SnH and $(TMS)_3SiH$, is key to the success of these relatively slow cyclizations. This method has been used to construct the left-hand fragment of the ciguatoxins.[151]

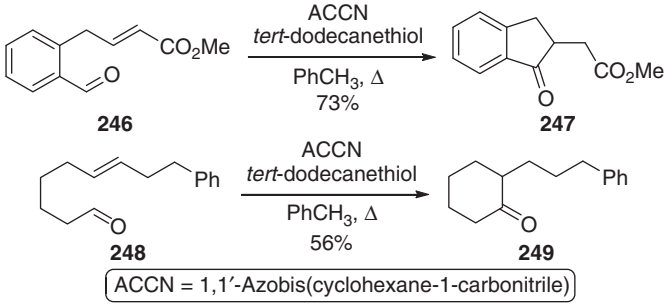


244a, *n* = 0
244b, *n* = 1

245a (76%)
245b (73%)

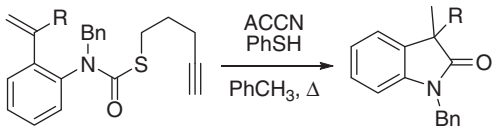
Scheme 68

Tomioka and coworkers have developed a convenient method of generating acyl radicals directly from aldehydes. The combination of a radical initiator (e.g., 1,1′-azobis(cyclohexane-1-carbonitrile), or ACCN) and odorless *tert*-dodecanethiol enables 5- and 6-*exo* cyclizations of aldehyde-derived acyl radicals onto both electron-deficient and unactivated alkenes (Scheme 69).[152] The bulkiness of the thiol prevents competitive thioacetal formation or conjugate addition from occurring.



Scheme 69

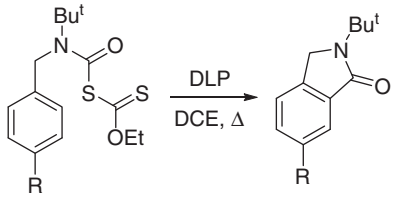
A tin-free protocol can be used to produce carbamoyl radicals from *S*-4-pentynyl carbamothioates. Treatment of these compounds with phenylthiol in the presence of a radical initiator causes thiyl radical addition to the alkyne followed by intramolecular homolytic substitution at the sulfur atom by the resulting vinyl radical. This substitution creates a carbamoyl radical, which can then undergo 5-*exo* cyclization to furnish a lactam (Scheme 70).[153] Carbamoylxanthates can also be employed as carbamoyl radical precursors, engaging in oxidative radical cyclizations onto aromatic rings (Scheme 71).[154]



250a, R = H
250b, R = Me

251a (67%)
251b (65%)

Scheme 70

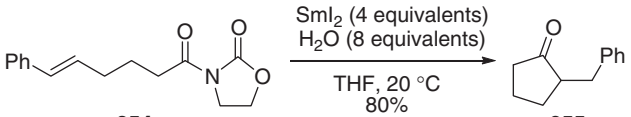


252a, R = CO_2Me
252b, R = Br
252c, R = OMe

253a (91%)
253b (92%)
253c (72%)

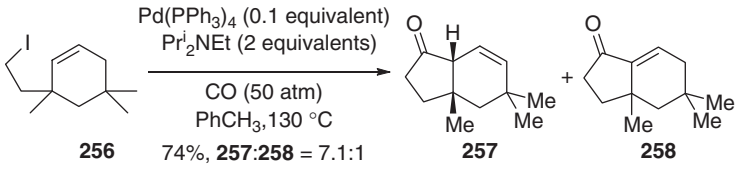
Scheme 71

The ketyl radical formed by exposure of *N*-acyl oxazolidinone **254** to SmI_2 functions as an acyl radical equivalent, and ketone **255** is produced in good yield as a result of 5-*exo* cyclization (equation 17).[155] Chiral α-branched substrates derived from asymmetric alkylation of Evans oxazolidinones can also cyclize, albeit in lower yields (45–50%).

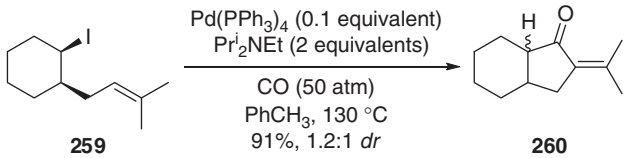


254 **255** (17)

The carbonylation of alkyl radicals has been used previously, most notably by Ryu and coworkers, as a means of generating acyl radicals.[156] Alexanian and Bloome have recently employed this technique in a Pd-catalyzed carbonylative Heck-type process with primary and secondary alkyl iodides (Scheme 72). Unlike typical Heck reactions, this process tolerates substrates with β-hydrogen atoms. The trapping of a putative alkyl radical intermediate with TEMPO provides evidence for a radical mechanism.[157]



256 **257** **258**

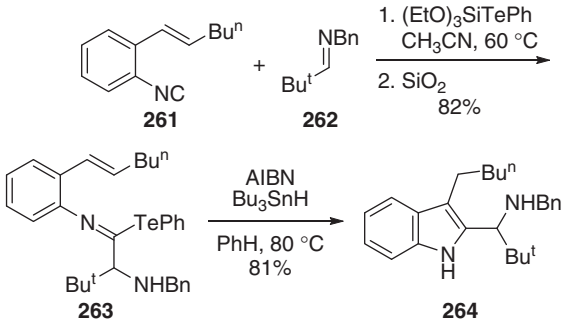


259 **260**

Scheme 72

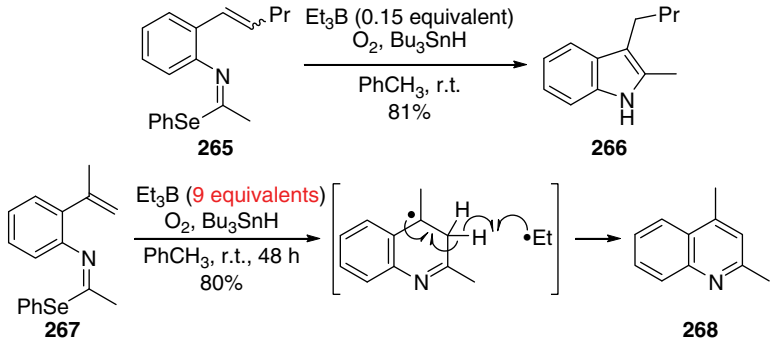
4.13.3.5.2 Imidoyl or iminyl radicals

The Fukuyama indole synthesis, which proceeds via the intermediacy of imidoyl radicals, is a valuable method for the construction of 3-substituted indoles.[158] 2,3-Disubstituted indoles are also accessible, but the standard protocol does not permit the construction of 2,3-dialkyl indoles. This problem has been solved by reacting α-aminomethyltellurides, which are formed by the addition of $(EtO)_3SiTePh$ to imines, with aryl isocyanides. The resulting imidoyltellurides are then treated with AIBN and Bu_3SnH to afford imidoyl radicals, which cyclize to deliver the desired 2,3-dialkyl indoles (equation 18).[159]



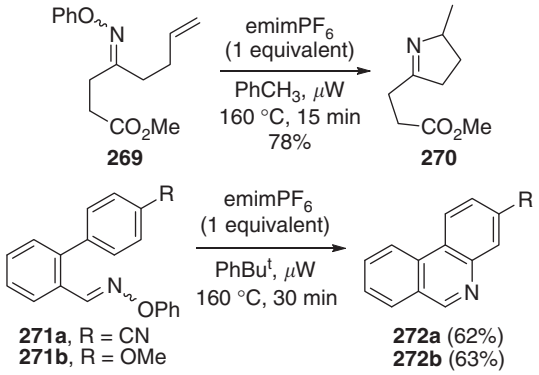
(18)

Bowman and coworkers have employed imidoyl selenides, which are derived from secondary amides via a two-step sequence, as imidoyl radical precursors. Substrates possessing a 1,2-disubstituted alkene (e.g., **265**) cyclize in a 5-*exo* fashion, providing indoles (e.g., **266**, Scheme 73). In contrast, use of a 1,1-disubstituted alkene as the radical acceptor switches the cyclization to a 6-*endo* pathway, affording quinolines after an oxidative aromatization process (e.g., **267**→**268**, Scheme 73). The requirement for excess Et_3B in the latter transformation is indicative of a nonchain process in which the initiator also participates in the aromatization step.[160]



Scheme 73

Thermolysis of *O*-phenyl oximes causes homolytic cleavage of the N–O bond, generating iminyl radicals. These species can cyclize onto alkenes and arenes, forming dihydropyrroles and various aromatic heterocycles such as phenanthridines (Scheme 74).[161] A small amount of an ionic liquid ($emimPF_6$) is employed to facilitate efficient microwave heating. The rapid

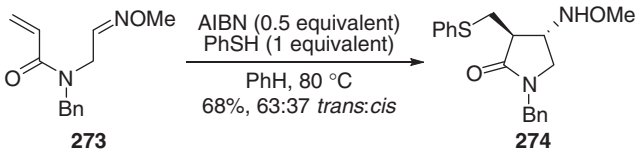


Scheme 74

reaction times and lack of toxic reagents or byproducts render this process attractive. Similar aromatic heterocycles are accessible by means of iminyl radical cyclizations initiated by photolyses of acyloximes,[162] dioxime oxalates,[163] and oxime carbonates.[164]

4.13.3.6 Heteroatom-Containing Radical Acceptors

Although most radical cyclizations involve carbon-based functional groups (i.e., alkenes, alkynes, or arenes) as acceptors, processes involving heteroatom-containing unsaturated functional groups have begun to emerge. Phenylthiyl radical adds selectively to the acrylamide moiety of substrate **273**, and the resulting α-carbonyl radical undergoes 5-*exo* cyclization onto the oxime ether, delivering functionalized lactam **274** with modest diastereoselectivity (equation 19).[165] Ketoxime ethers are viable acceptors for 6-*exo* vinyl radical cyclizations that are triggered by the addition of tributyltin radical to an alkyne (**Scheme 75**).[166] The ability to construct hindered *tert*-alkyl amine derivatives by this method is noteworthy. Analogous cyclizations initiated by thiyl radicals also occur, but in low yields.[167]



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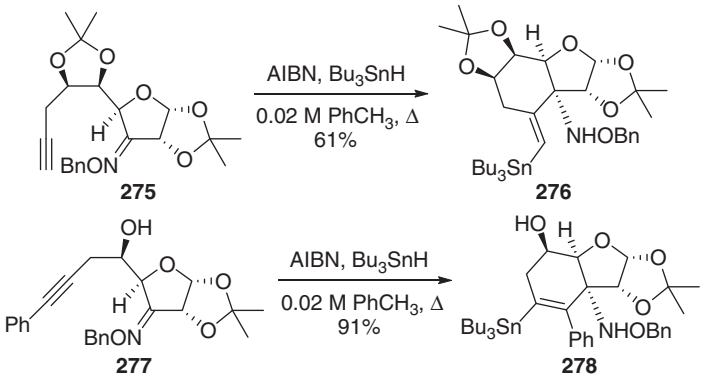
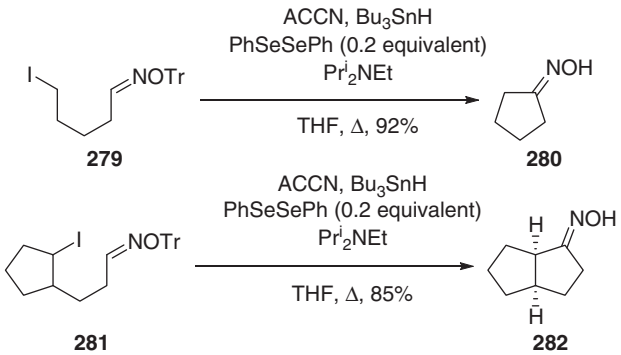


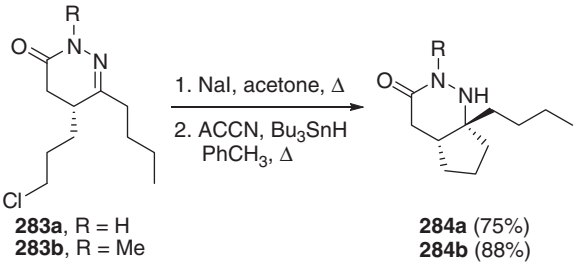
Scheme 75

Clive and coworkers have discovered an interesting radical cyclization with *O*-trityl oxime acceptors. The stable trityl radical is expelled on ring closure, and the resulting nitroso compound tautomerizes to afford an oxime (**Scheme 76**).[168] Hünig's base and diphenyl diselenide play critical roles in this reaction. The former promotes tautomerization, whereas the latter reacts with Bu_3SnH to generate PhSeH. The selenol reduces the trityl radical, preventing buildup of this persistent species from inhibiting cyclization. Preservation of the acceptor double bond in the product allows further synthetic manipulations.



Scheme 76

The pyridazinone ring system is a useful acceptor for 5-*exo* radical cyclizations (**Scheme 77**).[169] The stereoselective formation of congested *tert*-alkyl amine derivatives is notable. Reductive cleavage of the N–N bond permits additional functionalization of the adducts.

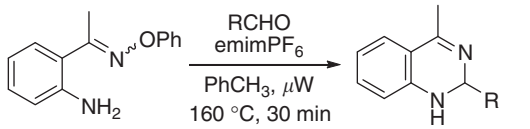


283a, R = H
283b, R = Me

284a (75%)
284b (88%)

Scheme 77

Dihydroquinazolines **286** are available from *O*-phenyl oxime **285** and aldehydes via a process that features ring closure of an iminyl radical onto an imine that is fashioned *in situ* (Scheme 78).[170] The lower yield observed with benzaldehyde is attributed to incomplete imine formation. If $ZnCl_2$ is used to promote this step, quinazolines are obtained instead of dihydroquinazolines.

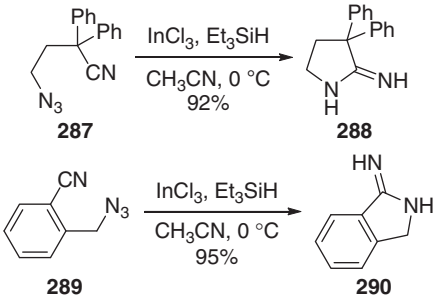


285

286a (R = Bu, 91%)
286b (R = Ph, 72%)

Scheme 78

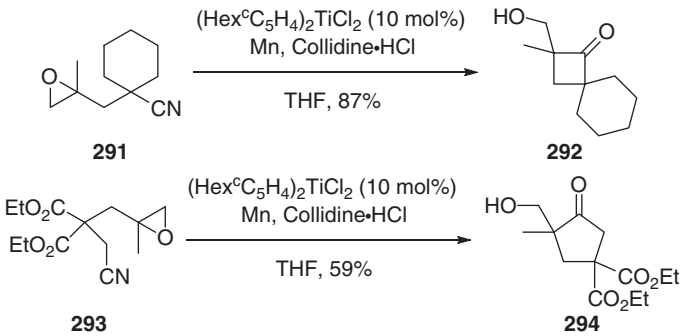
Nitriles are capable of engaging radicals in cyclization reactions. Nanni and coworkers have developed a tin-free protocol for creating nitrogen-centered radicals from azides. These species participate in 5-*exo* cyclizations, furnishing cyclic amidines (Scheme 79).[171] Inhibition of the reaction by TEMPO provides evidence for a radical pathway. Radicals derived from titanocene-mediated epoxide opening can also cyclize onto nitriles, yielding cyclobutanones and cyclopentanones after hydrolysis of the intermediate imine (Scheme 80).[172] The catalyst structure is critical to the success of the process, as both larger and smaller titanocenes are unsuitable.



287 **288**

289 **290**

Scheme 79

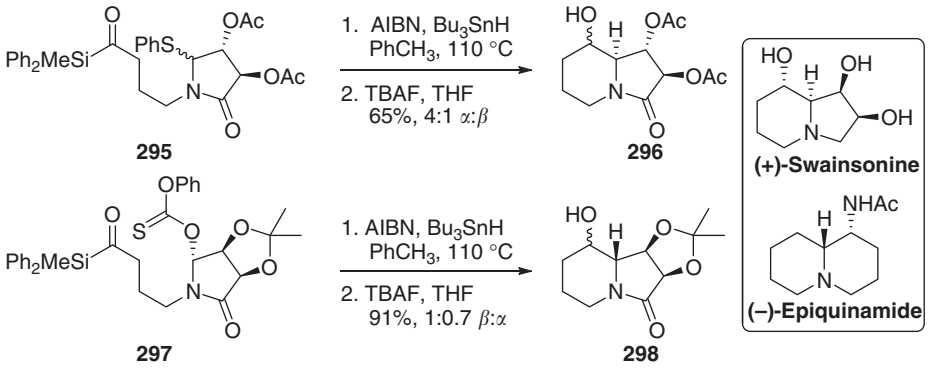


291 **292**

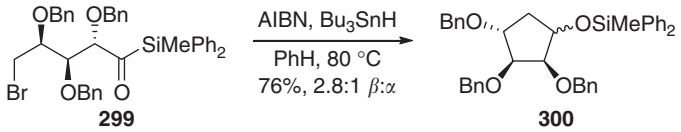
293 **294**

Scheme 80

Tsai and coworkers have studied radical cyclizations with acylsilane acceptors. The oxygen-centered cyclic radical intermediate undergoes a radical-Brook rearrangement, producing a silyloxy-substituted carbon radical that is reduced by Bu_3SnH. Formation of the strong Si–O bond provides a thermodynamic driving force for the entire process. Phenyl sulfides (i.e., **295**) and thiocarbonates (**297**) are suitable precursors for α-acylamino radicals that engage pendant acylsilanes in 6-*exo* cyclizations, producing adducts **296** and **298** with excellent diastereoselectivity at the bridgehead carbon (Scheme 81).[173] This method has been employed to construct the alkaloids (+)-swainsonine and (–)-epiquinamide.[174] The 5-*exo* cyclizations of carbohydrate-derived acylsilanes deliver highly oxygenated cyclopentanes with modest 1,2-*cis* diastereoselectivity (equation 20).[175]

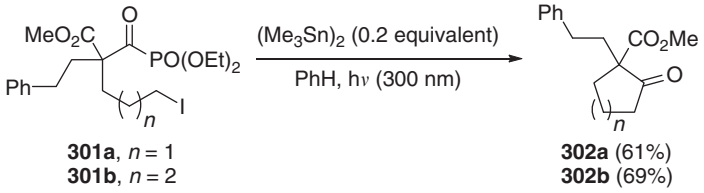


Scheme 81



(20)

Acylphosphonates can serve as radical acceptors, and the resulting alkoxy radicals undergo β-elimination of a phosphonate radical, producing cyclic ketones (Scheme 82).[176] As the phosphonate radical is capable of abstracting an iodine atom from an alkyl halide, catalytic quantities of the ditin reagent can be utilized. Acylphosphonates are superior to acylgermanes and thioesters in this reaction.



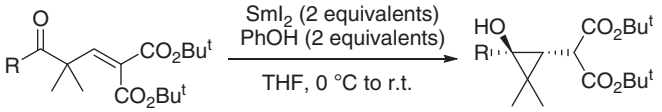
Scheme 82

4.13.4 Cyclizations That Form Unusual-Sized Rings

The most common radical cyclizations generate 5- or 6-membered rings. Nevertheless, it is also possible to construct both small- and medium-sized rings using radical methods. The slower rates of these less-common processes present significant challenges that have been overcome by using certain reagents (e.g., SmI_2 and titanocenes) or substrates. In this section, cyclizations that form unusual-sized rings are discussed.

4.13.4.1 3–4-Membered Rings

SmI_2-mediated 3-*exo*-*trig* ketyl radical cyclizations are useful for synthesizing cyclopropanols. Di-*tert*-butyl alkylidene malonates **303** undergo cyclization to afford *trans* cyclopropanols **304** exclusively (Scheme 83).[177] The use of phenol as the proton source was key to achieving high diastereoselectivity, as reactions employing *tert*-butanol afforded mixtures of *trans* and *cis* isomers.

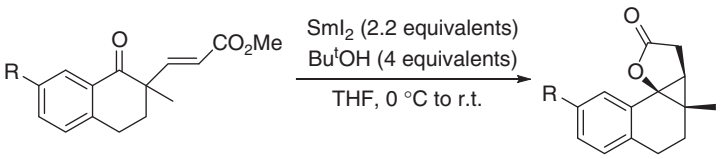


303a, R = Me
303b, R = Ph
303c, R = Bn

304a (85%)
304b (70%)
304c (98%)

Scheme 83

In contrast, tetralones **305** cyclize with *cis* selectivity in the presence of *tert*-butanol, and the resulting adducts undergo spontaneous lactonization to furnish tetracycles **306** (Scheme 84).[178]

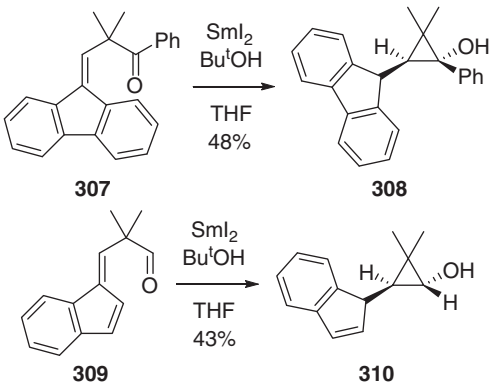


305a, R = H
305b, R = OMe

306a (93%)
306b (78%)

Scheme 84

The vast majority of SmI_2-promoted 3-*exo* cyclizations involve enoate or alkylidene malonate acceptors. Recently, Ortiz and Armesto have extended this process to include flourenyl- and indenyl-containing substrates (Scheme 85), which presumably afford stabilized anionic intermediates on cyclization and subsequent reduction.[179] The *trans* cyclopropanols are obtained exclusively.



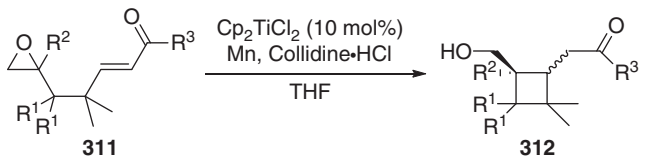
307 **308**

309 **310**

Scheme 85

Titanocene-catalyzed 4-*exo* cyclizations of epoxides **311** furnish cyclobutanes **312** in good yields (Table 16).[180] In some cases, bulkier catalysts give improved diastereoselectivities. The use of cationic catalyst **314** allows for cyclizations of substrates devoid of

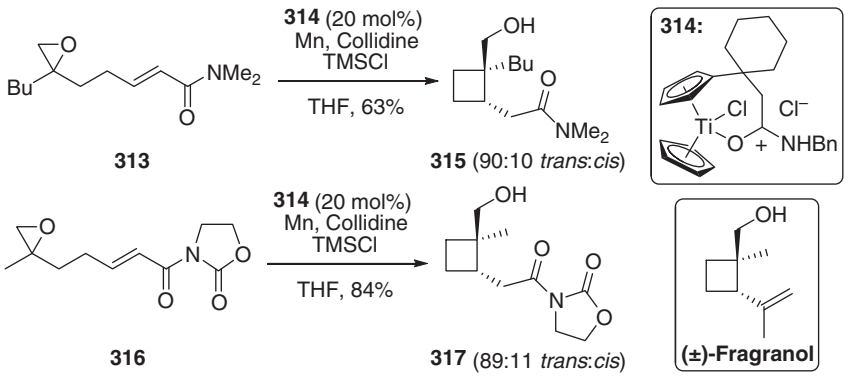
Table 16 Ti-catalyzed 4-*exo* cyclizations



311 **312**

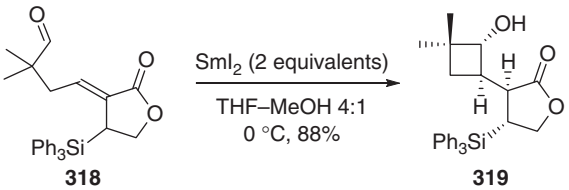
Entry	R^1	R^2	R^3	*Yield (%)*	*trans:cis*
1	H	Me	OBu^t	82	67:33
2	H	Me	NMe_2	92	83:17
3	Me	H	OBu^t	88	90:10
4	Me	H	NMe_2	81	89:11

gem-dialkyl substitution (i.e., **313**→**315** and **316**→**317**, Scheme 86).[181] It is postulated that two-point binding of the intermediate acyclic radicals to the catalyst via the alkoxy and carbonyl groups facilitates these challenging ring closures. Cyclobutane **317** has been utilized as an intermediate in the synthesis of (±)-fragranol.[182]



Scheme 86

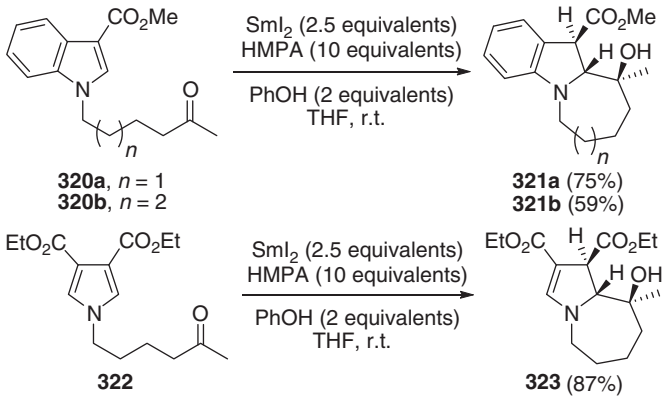
Procter and coworkers have developed SmI_2-mediated 4-*exo*-*trig* cyclizations for the preparation of cyclobutanols,[183] but attempts to use a silyl ether as a stereocontrol element were only modestly successful.[184] This problem has been solved by employing a silyl substituent bound directly to carbon (equation 21).[185] Enantioenriched substrates analogous to **318** are readily available. The versatility of the C–Si bond as a handle for further transformations adds to the utility of this process.



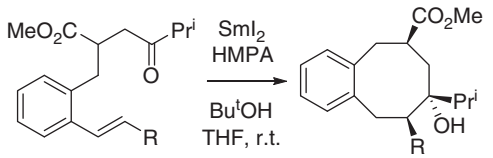
(21)

4.13.4.2 7–9-Membered Rings

Reissig and coworkers have introduced several types of SmI_2-promoted cyclizations that are useful for synthesizing medium-sized rings. Indoles **320** and pyrrole **322**, which contain electron-withdrawing carboalkoxy groups, cyclize to furnish products that contain seven- and eight-membered rings (Scheme 87).[186] The excellent diastereocontrol is attributed to a transition state in which the samarium(III) alkoxide resides in a pseudoequatorial position. Benzannulated cyclooctanols are accessible via regio- and stereoselective 8-*endo* cyclizations of keto styrenes **324** (Scheme 88).[187] The yield decreases with increasing size of the styrene substituent, but useful quantities of the cyclooctanol product are still obtained from phenyl-substituted substrate **324c**. Analogous 9-*endo* and 10-*endo* cyclizations are also feasible, albeit with reduced levels of stereoselectivity (Scheme 89).[188] The major *cis* isomer of the 9-*endo* ring closure spontaneously lactonizes to afford a bridged tricyclic compound.



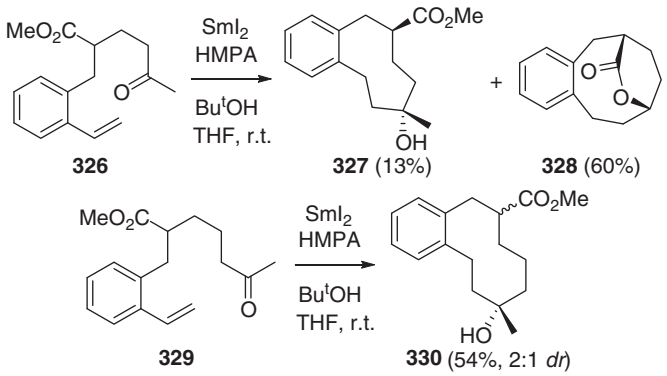
Scheme 87



324a, R = H
324b, R = Me
324c, R = Ph

325a (84%)
325b (63%)
325c (47%)

Scheme 88



326

327 (13%)

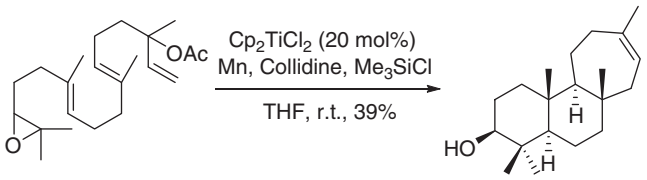
328 (60%)

329

330 (54%, 2:1 *dr*)

Scheme 89

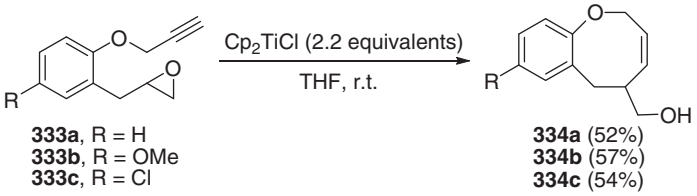
Titanocene(III) species are capable of facilitating the formation of medium-sized rings. In a cascade reaction that features a 7-*endo* cyclization, exposure of epoxide **331** derived from geranyl-linalyl acetate to a titanocene(III) catalyst that is generated *in situ* delivers tricycle **332** (equation 22).[189] Although the overall yield is modest, three rings and five stereocenters including two all-carbon quaternary stereocenters are fashioned in a single transformation. Presumably, the bulky acetate-bearing allylic carbon favors the 7-*endo* pathway by slowing the corresponding 6-*exo* process. Eight-membered cyclic ethers **334** are available via 8-*endo* cyclizations of substrates **333**, which pair epoxide radical precursors with alkyne acceptors (Scheme 90).[190] An excess of titanocene(III) chloride is required to promote these reactions.



331

332

(22)



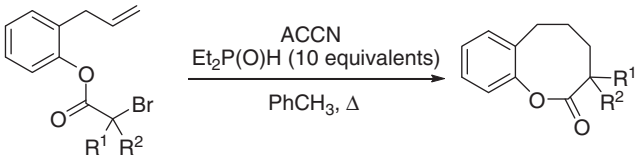
333a, R = H
333b, R = OMe
333c, R = Cl

334a (52%)
334b (57%)
334c (54%)

Scheme 90

Diethylphosphine oxide can mediate 8-*endo* cyclizations of α-bromo esters **335**, affording lactones **336** (Scheme 91).[191] *N*-ethylpiperidinium hypophosphite (EPHP) can be used in place of $Et_2P(O)H$ with similar results, but this transformation does not work cleanly with Bu_3SnH. The use of amides instead of esters results in mixtures of seven- and eight-membered lactams.

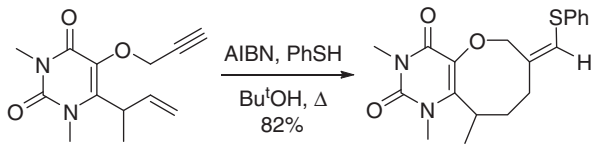
Majumdar and coworkers have investigated thiophenol-triggered vinyl radical cyclizations. The 8-*endo* process is facile, and cyclic ethers annulated to both heterocycles (Scheme 92)[192] and benzenes (Scheme 93)[193] are accessible. The reasons for the contrasting stereoselectivity (*Z*-isomers with heterocycles, *E*-isomers with benzenes) are unclear. The use of styrenes instead of



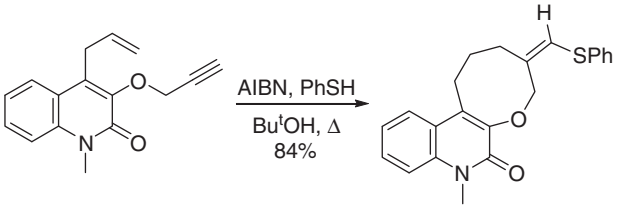
335a; $R^1 = R^2 = H$
335b; $R^1 = Me$, $R^2 = H$
335c; $R^1 = R^2 = Me$

336a (80%)
336b (91%)
336c (64%)

Scheme 91

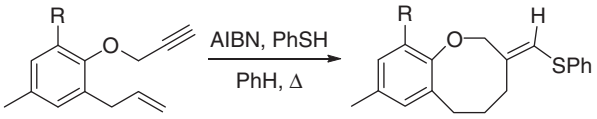


337 **338**



339 **340**

Scheme 92

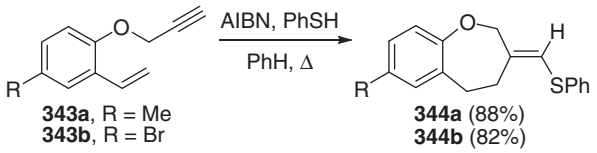


341a, R = H
341b, R = Me

342a (85%)
342b (80%)

Scheme 93

allylbenzenes as substrates leads to oxepins by means of a 7-*endo* cyclization (Scheme 94).[194] The formation of a stabilized benzylic radical is believed to favor the 7-*endo* pathway over the 6-*exo* alternative.



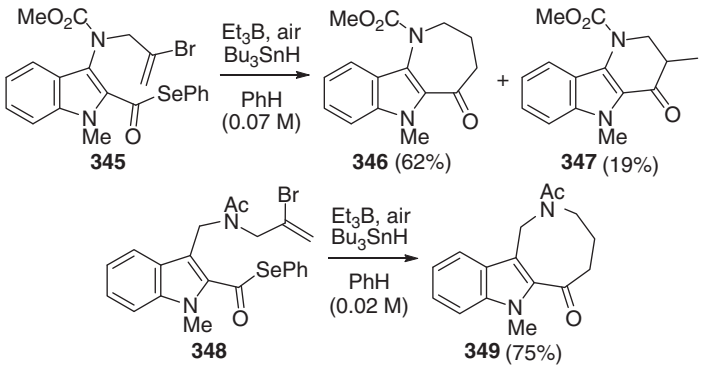
343a, R = Me
343b, R = Br

344a (88%)
344b (82%)

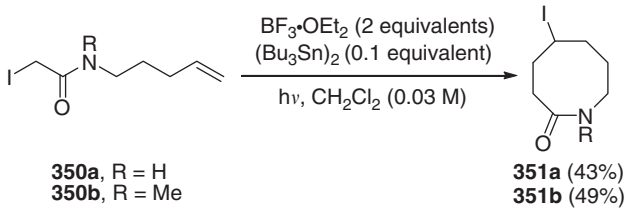
Scheme 94

2-Indolylacyl radicals participate in 7- and 8-*endo* cyclizations, furnishing tricyclic adducts **346** and **349** in good yields (Scheme 95).[195] A vinyl bromide is used as a temporary regiodirecting group to enforce the desired *endo* ring closure over the alternative *exo* process. An excess of Bu_3SnH causes reduction of the bromide after cyclization has occurred. Dilute conditions are sometimes necessary to prevent reduction of the acyl radical before cyclization.

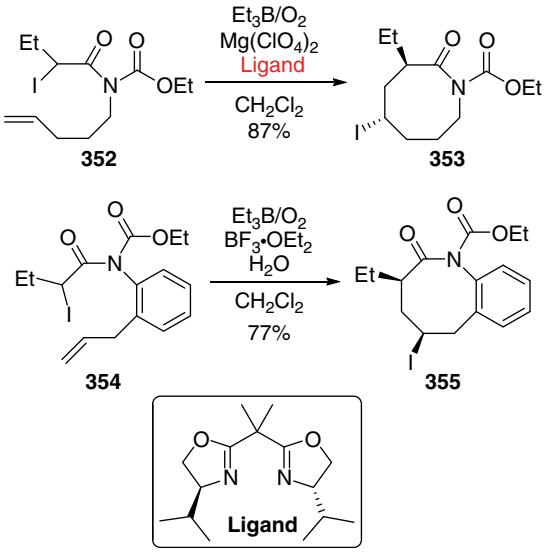
Li and coworkers have studied the 8-*endo* atom transfer radical cyclizations of α-iodo amides. The use of $BF_3 \cdot OEt_2$ as a Lewis acid enables successful cyclizations of amides **350** (Scheme 96).[196] The carbamate group of substrates **352** and **354** provides an opportunity for Lewis acid chelation to fix the acyclic radicals in the s-*cis* conformation, which is most productive for efficient and stereoselective cyclizations (Scheme 97).[197] Interestingly, $Mg(ClO_4)_2$ is the optimal Lewis acid for cyclization of alkyl-tethered substrate **352**, and a bisoxazoline ligand is required for it to dissolve in CH_2Cl_2. *Trans* stereochemistry is observed exclusively in the racemic product **353**. In contrast, $BF_3 \cdot OEt_2$ is the best Lewis acid for cyclization of phenyl-tethered substrate **354**, and *cis* lactam **355** is produced.



Scheme 95



Scheme 96

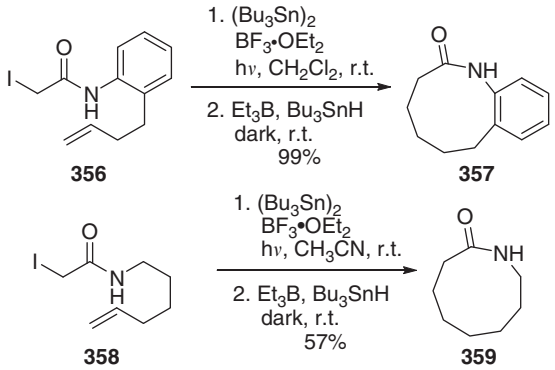


Scheme 97

Nine-membered lactams are also accessible via the atom transfer radical cyclization method. In this case, reduction of the unstable γ-iodo lactam cycloadducts is performed immediately, affording azonan-2-ones **357** and **359** (Scheme 98).[198] Alternatively, treatment of the crude products with Na_2CO_3 induces transannular nucleophilic substitution, providing hexahydroindolizinones.

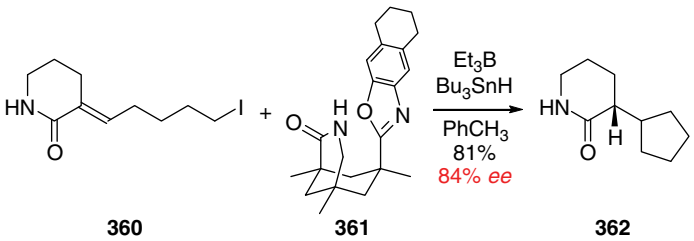
4.13.5 Enantioselective Cyclizations and Chirality Transfer

Enantioselective radical cyclizations[4] are less common than enantioselective intermolecular radical additions.[5] Nevertheless, recent reports suggest that this field is growing in importance. Also of interest are cyclizations involving the transfer of chirality from an axially chiral radical to a newly formed stereocenter in the product. Bach and coworkers have achieved enantioselective

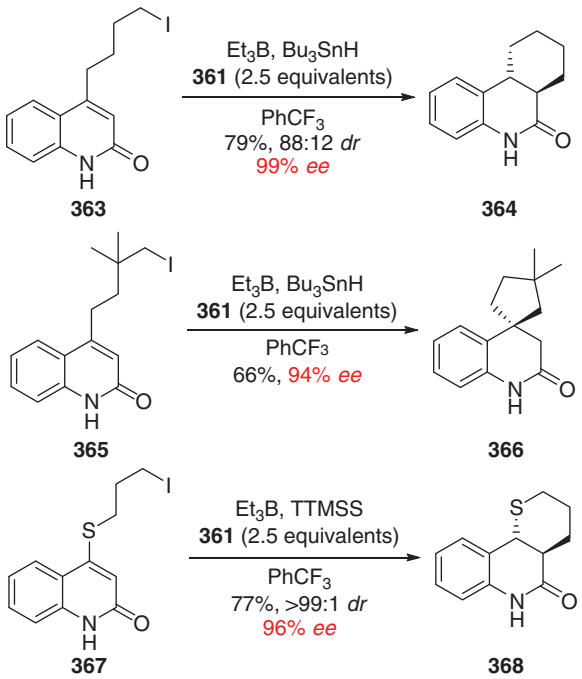


Scheme 98

radical cyclization of lactam **360** by use of the chiral complexing agent **361**, which activates the substrate by hydrogen bonding and enables enantioselective hydrogen atom abstraction (Scheme 99).[199] Further investigation has shown that use of trifluorotoluene as solvent improves the diastereo- and enantioselectivity of the 6-*endo* cyclization of quinolone **363** (Scheme 100).[200] Interestingly, neopentylic iodide **365** undergoes 5-*exo* spirocyclization instead. In the reaction of sulfide **367**, the use of TTMSS as the hydrogen atom donor is key to achieving a high yield.[201] Surprisingly, TTMSS-mediated cyclizations of substrates **363** and **365** are low yielding.

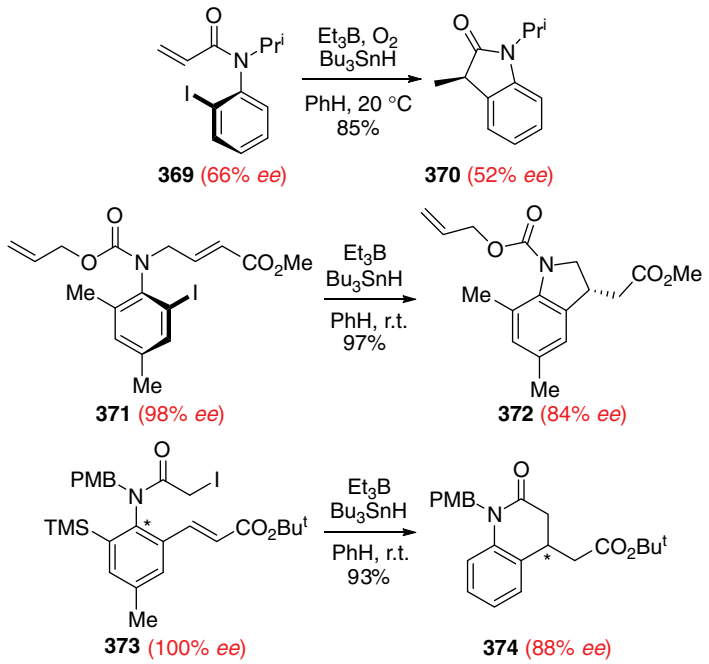


Scheme 99



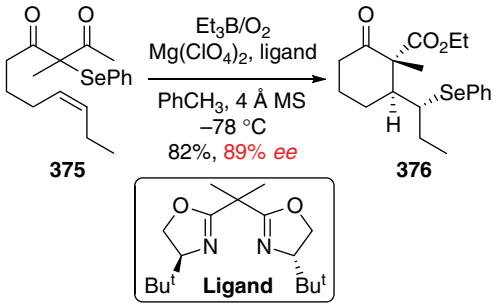
Scheme 100

Curran and coworkers have explored radical cyclizations of *o*-iodoaryl acrylanilides, which exist as pairs of resolvable atropisomers (ΔG for racemization is ca. 23 kcal mol^{-1}). The cyclization of anilide **369** proceeds with 91% chirality transfer (Scheme 101).[202] Axially chiral carbamates (e.g., **371**)[203] and *o*-alkenyl anilides (e.g., **373**)[204] also cyclize in high yields with excellent levels of chirality transfer.



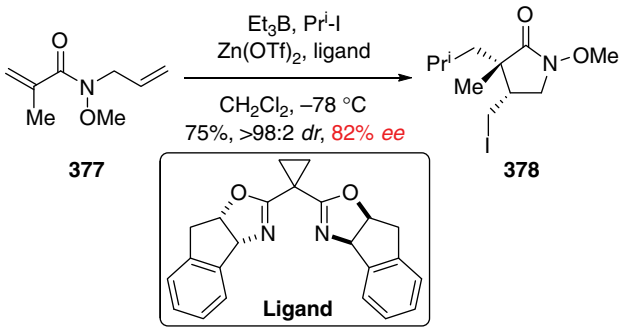
Scheme 101

Enantioselective group-transfer radical cyclization of α-phenylselenide **375** can be accomplished with a chiral Mg–bisoxazoline Lewis acid (equation 23).[205] The transformation is most selective in the presence of a stoichiometric amount of the Lewis acid. Tandem cyclizations are also feasible, but with appreciable drops in yield and *ee*.



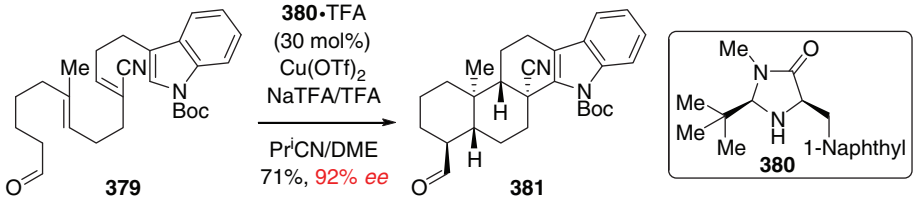
(23)

Miyabe, Takemoto, and coworkers have reported an enantio- and diastereoselective radical addition–cyclization–trapping process with *N*-methoxy amide **377** (equation 24).[206] The methoxy group is thought to enable chelation of the chiral Lewis acid. Good results can also be obtained with an oxime ether acceptor in place of the terminal alkene.[207] Additionally, enantioselective perfluoroalkylation can be achieved by this method, albeit with reduced levels of diastereoselectivity. Interestingly, the latter transformation is initiated by a polarity-mismatched addition of the electrophilic perfluoroalkyl radical to an electron-deficient radical acceptor.[208]

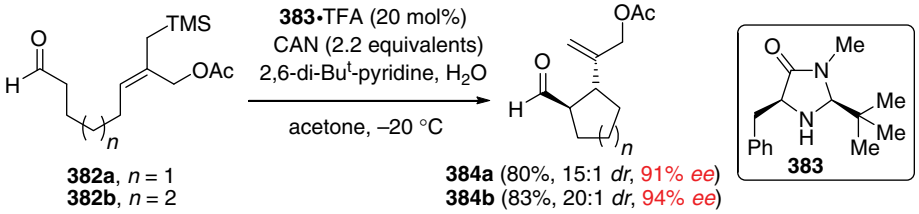


(24)

MacMillan and coworkers have utilized the organo-singly occupied molecular orbital (SOMO) catalysis concept to accomplish enantioselective radical cyclizations. When aldehyde **379** engages imidazolidinone **380** in the presence of $Cu(OTf)_2$, the ensuing chiral radical cation undergoes a cyclization cascade followed by a terminating one-electron oxidation to deliver pentacycle **381** in good yield and *ee* (equation 25). The process can be extended to form up to six new carbon–carbon bonds with the generation of 11 contiguous stereocenters, five of which are quaternary.[209] An intramolecular enantioselective α-allylation of aldehydes is also possible using organo-SOMO catalysis. Five- and six-membered rings are accessible in highly diastereo- and enantioselective fashion (Scheme 102).[210]



(25)



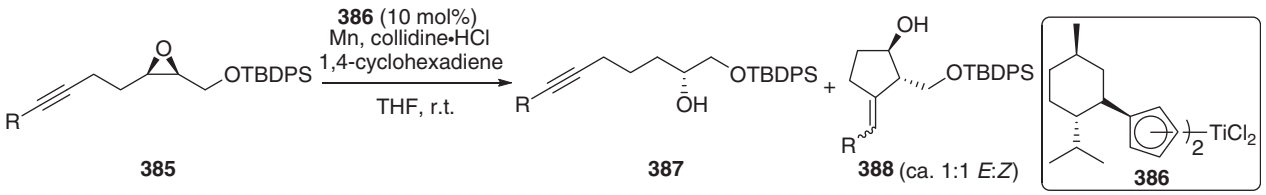
Scheme 102

Gansäuer and coworkers have developed an unusual enantioselective radical cyclization that capitalizes on a regiodivergent epoxide ring-opening process. When racemic epoxides **385** are exposed to chiral titanocene catalyst **386**, the two enantiomers undergo ring opening at different sites, furnishing regioisomeric radicals of opposite chirality. One radical is reduced to provide enantioenriched alcohol **387**, as the alternative 4-*exo*-*dig* cyclization is not favored. In contrast, the other regioisomer participates in a highly diastereoselective 5-*exo*-*dig* ring closure, producing methylenecyclopentanes **388** with high *trans* selectivity and excellent *ee* (Table 17).[211] The mixture of *E*- and *Z*-isomers converges to afford a single cyclopentane after hydroxyl-directed hydrogenation.

4.13.6 Sequential Radical Reactions

One of the virtues of radical chemistry is its amenability to tandem or cascade processes.[22,23] In some cases, multiple radical steps are sequenced in a one-pot transformation, whereas others involve a combination of radical and polar steps (i.e., radical-polar crossover reactions). Both types of cascades represent valuable methods of constructing complex molecules from relatively simple precursors in rapid fashion. Sequential radical reactions and radical-polar crossover reactions are most useful when they proceed stereoselectively. Owing to the large number of significant recent discoveries in this area, this section is divided into subsections based on the organizational pattern of the chapter. Although the overall focus of the chapter is on radical cyclizations, this section contains selected examples of all-intermolecular sequential radical reactions.

Table 17 Enantioselective cyclizations based on regiodivergent epoxide ring-opening

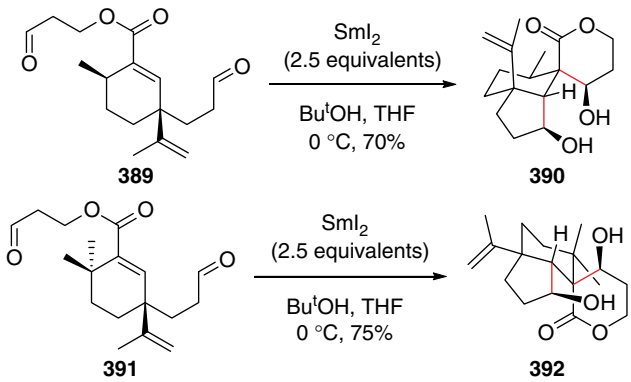


Entry	*R*	*Yield of **387** (%)*	*ee of **387** (%)*	*Yield of **388** (%)*	*trans:cis of **388***	*ee of **388** (%)*
1	Et	38	77	38	91:9	94
2	CH_2OTES	36	70	25	91:9	95
3	CO_2Me	47	71	33	91:9	95
4	Ph	46	76	36	97:3	95

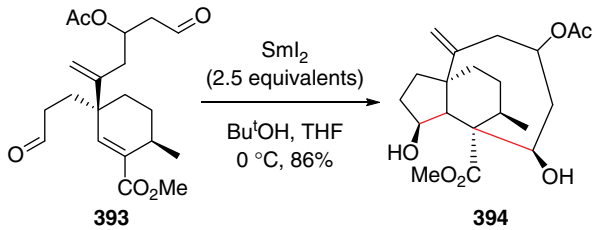
4.13.6.1 Tin-Free Processes Involving Carbon-Centered Radicals

4.13.6.1.1 Reactions mediated by metals other than tin

Procter and coworkers have developed a variety of SmI_2-mediated cascade transformations, including a highly diastereoselective process consisting of ketyl radical cyclization followed by intramolecular aldol reaction (Scheme 103).[212] The use of an enoate radical acceptor enables the formation of an enolate after the initial cyclization via single-electron reduction. The regioselective ketyl radical formation may be attributed to a reversible process where only one of the two possible radicals can cyclize, or to activation of the reactive aldehyde by coordination to SmI_2. Interestingly, geminal dimethyl-substituted substrate **391** exhibited reversed facial selectivity in the aldol cyclization relative to methyl-substituted congener **389**. The facile stereoselective construction of tricycle **394**, which involves the formation of an eight-membered ring, is notable (equation 26).[213]

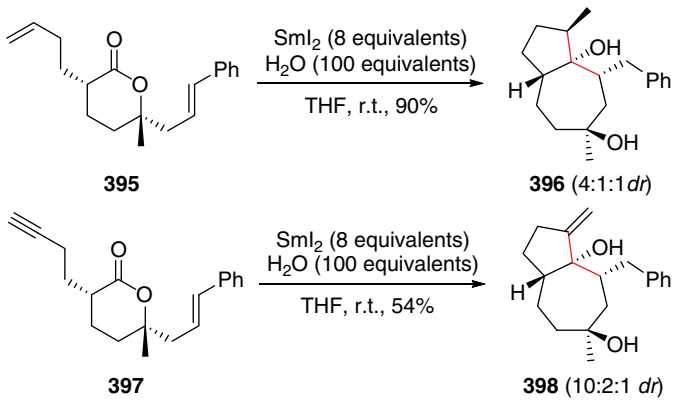


Scheme 103



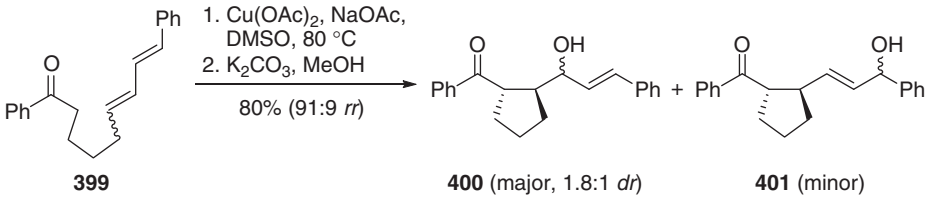
(26)

The use of H_2O as an activating cosolvent permits the reduction of lactones by SmI_2. The resulting radical anions can participate in tandem cyclizations, as exemplified by the conversions of lactones **395** and **397** into azulenes **396** and **398** (Scheme 104).[214] Calculations suggest that the first cyclization occurs onto the phenyl-substituted alkene, and the resulting bridged bicyclic hemiketal then collapses to afford a ketone. Reduction of the ketone by the excess SmI_2 and subsequent cyclization delivers the azulene products.



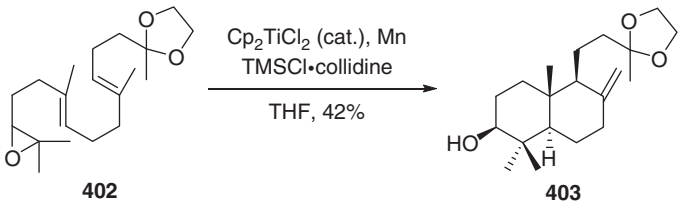
Scheme 104

Dienone **399** undergoes regioselective cyclization–acetoxylation when exposed to $Cu(OAc)_2$, and cyclopentane **400** is produced in good yield on hydrolysis of the intermediate acetate (equation 27).[215] Whereas cyclization is quite likely to be a radical process, the subsequent acetoxylation may proceed via an allylic radical or cation intermediate.

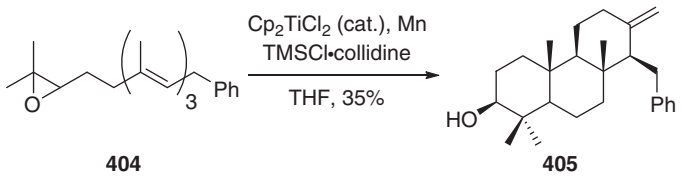


(27)

The titanocene-catalyzed ring opening of epoxides can be used to initiate tandem cyclizations of polyenes (equation 28) (*see* Chapter 3.05).[216] Although the yield of bicycle **403** is modest, the product is obtained as a single regio- and diastereomer. Tricyclization cascades are also possible (equation 29).[217] A related diastereoselective process involving stoichiometric quantities of Ti(III) is terminated by 4-*exo* radical cyclization onto a nitrile acceptor (**Scheme 105**).[218] The corresponding 5-*exo* and 6-*exo* cyclizations proceed with lower yields.

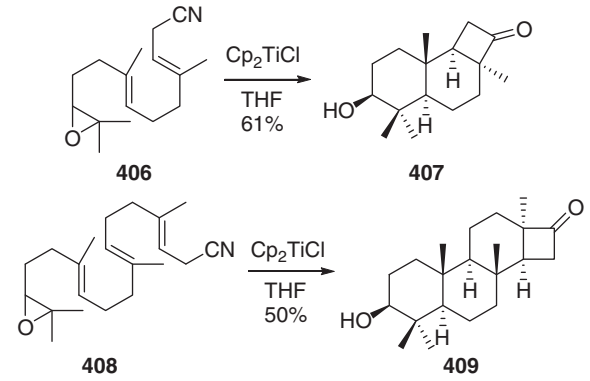


(28)

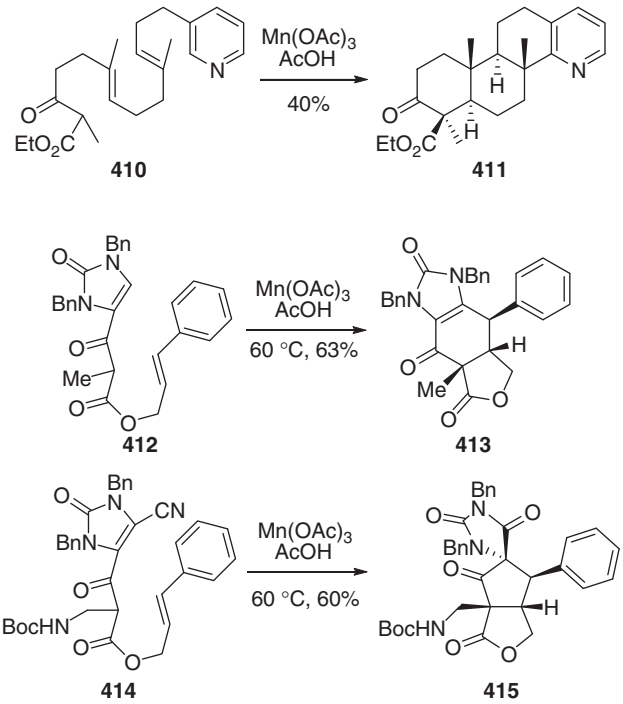


(29)

Polyene cyclizations can also be initiated via $Mn(OAc)_3$-mediated oxidation of β-keto esters (equation 30).[219] Interestingly, an alkyl radical attacks the pyridine ring at C-2 rather than C-4 in the final cyclization step. The cores of two different pyrrole–imidazole alkaloid families can be fashioned via Mn(III)-promoted tandem cyclizations. β-Ketoester **412** undergoes stereoselective 5-*exo*/6-*exo* cyclization to deliver the ageliferin/nagelamide core skeleton **413**, whereas the cyano group of substrate **414** directs the second ring closure down a 5-*exo* pathway before suffering oxidative fragmentation (**Scheme 106**).[220] The resulting spirocycle **415** possesses the core structure of massadine, palau'amine, and axinellamine.



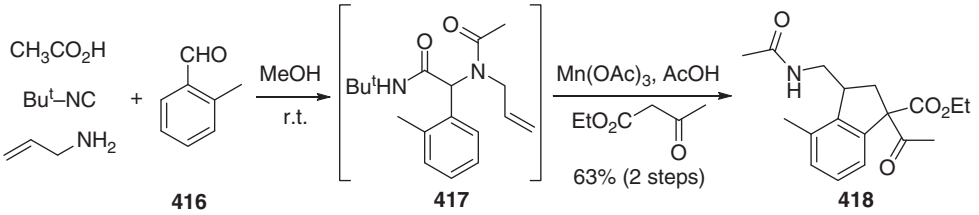
Scheme 105



(30)

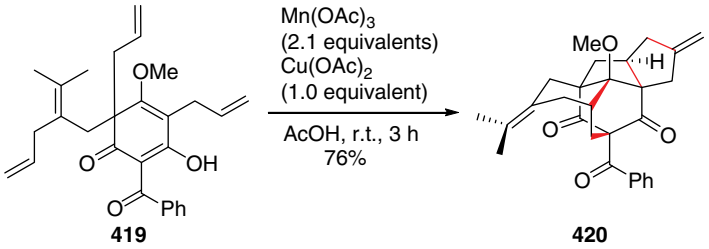
Scheme 106

Highly substituted indanes are available via an unusual $Mn(OAc)_3$-promoted cascade radical process. Treatment of *o*-methylbenzaldehyde (**416**) with acetic acid, *tert*-butyl isocyanide, and allylamine generates Ugi adduct **417**, and evaporation of the solvent followed by addition of $Mn(OAc)_3$ and ethyl acetoacetate in refluxing acetic acid furnishes indane **418** (Scheme 107).[221] The reaction is believed to proceed by intermolecular addition of the acetoacetyl radical to the *N*-allyl group, followed by 1,4-aryl transfer and fragmentation of the *tert*-butyl amide. The formation of a second *β*-keto ester radical and 5-*exo*-*trig* cyclization onto the aryl ring delivers the final product.



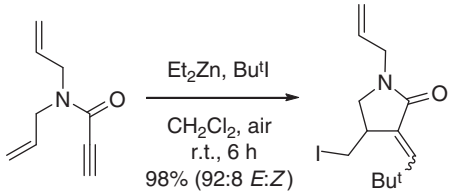
Scheme 107

Mitasev and Porco[222] have utilized $Mn(OAc)_3$ to facilitate a formal [4 + 2] cycloaddition of dearomatized phloroglucinol **419** that delivers bicyclo[2.2.2]octadione **420** (equation 31). The ability to construct four rings in a single step with high yield is noteworthy.

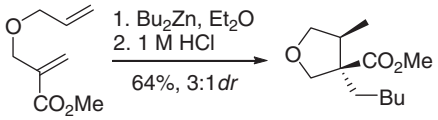


419 **420** (31)

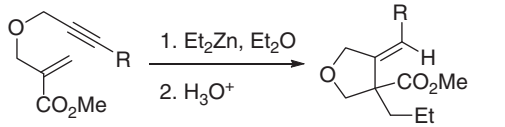
Diethylzinc promotes the sequential radical addition–cyclization-iodine atom transfer of amide **421** and *tert*-butyl iodide (equation 32).[223] In the final step, iodine atom transfer is favored over reductive zincation. Substituted furans can be synthesized by similar processes involving alkenes (equation 33),[224] internal alkynes (Scheme 108),[225] and terminal alkynes (Scheme 109)[226] as acceptors in the cyclization step. These latter reactions are terminated by protonation of an alkyl- or vinylzinc species.



421 **422** (32)



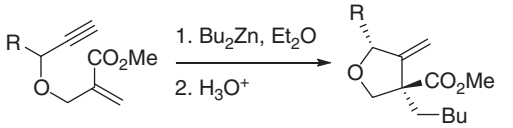
423 **424** (33)



425a, R = TMS
425b, R = Ph

426a (91%, >95:5 *Z*:*E*)
426b (79%, 90:10 *Z*:*E*)

Scheme 108

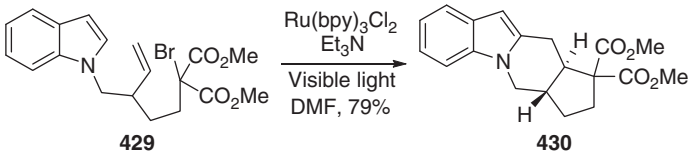


427a, R = pentyl
427b, R = Ph

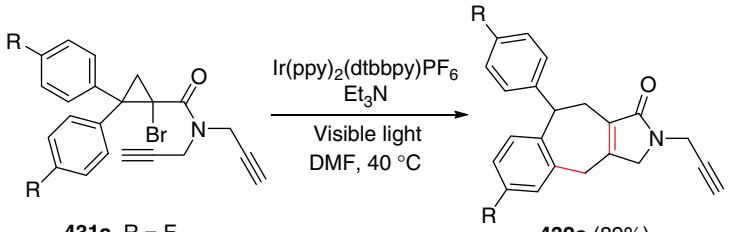
428a (60%, 3:1 *dr*)
428b (59%, 7:3 *dr*)

Scheme 109

Stephenson and coworkers have developed cascade processes featuring Ru(II) and Ir(III) photoredox catalysis. Exposure of indole **429** to $Ru(bpy)_3Cl_2$ and visible light triggers a tandem radical cyclization, delivering tetracycle **430** as a single isomer (equation 34).[227] Irradiation of bromocyclopropanes **431** in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ induces a radical cyclization–divinylcyclopropane rearrangement sequence, producing tricyclic pyrrolidinones **432** (Scheme 110).[228]



429 430 (34)



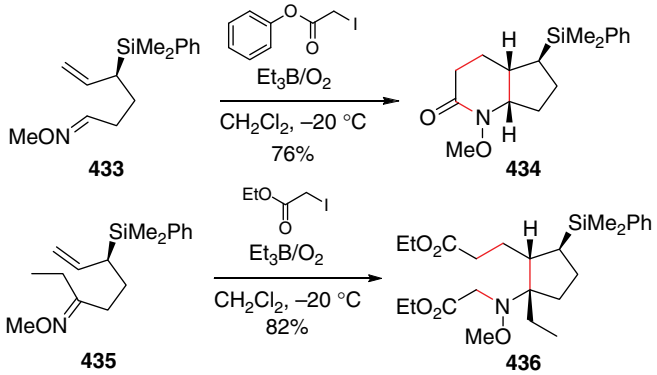
431a, R = F
431b, R = OMe

432a (89%)
432b (79%)

Scheme 110

4.13.6.1.2 Metal-free reactions

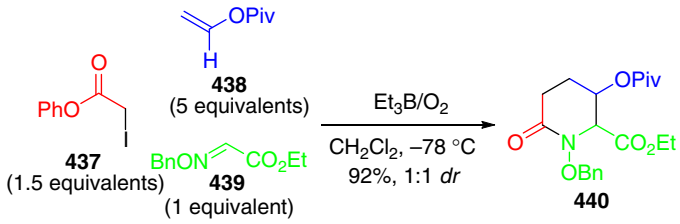
Highly substituted piperidinones are available via two closely related metal-free radical-polar crossover reactions. Both phenyl and ethyl iodoacetates produce radicals in the presence of triethylborane and oxygen. Radicals generated from α-iodoacetates undergo intermolecular addition onto the allylsilane double bond of substrate **433**, and a 5-*exo*-*trig* cyclization ensues. The resulting nitrogen-centered radical reacts with Et_3B to form a nucleophilic amido–borane complex, which lactamizes to produce piperidinone **434** (Scheme 111).[229] When a ketoxime is employed instead of an aldoxime, the second cyclization does not occur, and a radical recombination process leads to cyclopentane **436** instead. A three-component coupling in which the alkene and oxime moieties are not tethered allows synthesis of monocyclic piperidinones (equation 35).[230]



433 **434**

435 **436**

Scheme 111

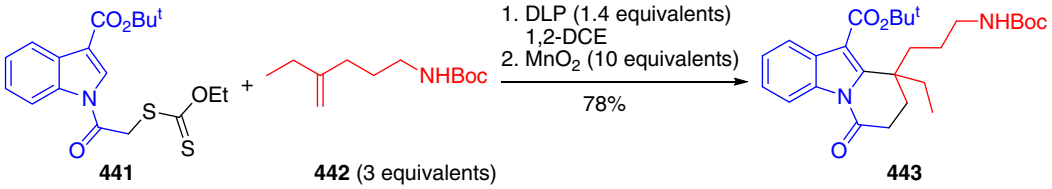


437 (1.5 equivalents) **438** (5 equivalents) **439** (1 equivalent)

440 (35)

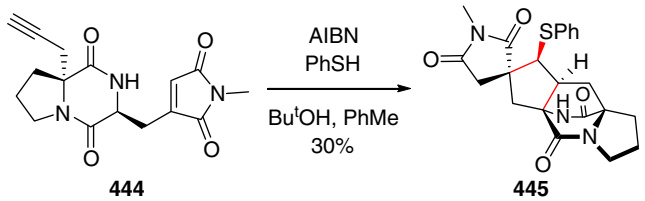
A metal-free radical annulation can be used to construct polycyclic indoles in a convergent fashion. Treatment of xanthate **441** with DLP in the presence of alkene **442** affords indole **443** (equation 36).[231] A minor amount of dihydroindole is formed by

disproportionation, and the treatment of the crude reaction mixture with MnO_2 promotes aromatization of this byproduct. Compound **443** is an intermediate in a formal total synthesis of (±)-mersicarpine.[231]



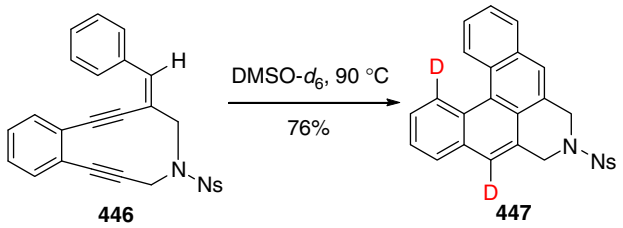
(36)

A metal-free radical cascade has been used to transform diketopiperazine **444** into pentacycle **445**, which contains the core structure of the asperparaline family of alkaloids (equation 37).[232] The reaction is likely to proceed via the phenylthiyl radical addition to the alkyne, 1,6-hydrogen atom transfer, and consecutive 6-*exo-trig* and 5-*exo-trig* cyclizations. The modest yield is mitigated somewhat by the excellent diastereoselectivity.



(37)

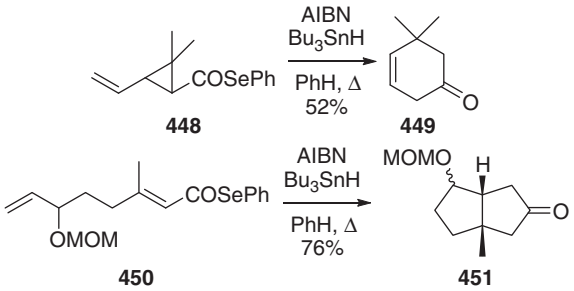
The Bergman cyclization, which has been underutilized as a synthetic method, can be incorporated into a radical cascade that forges angularly fused aromatic compounds. When enediyne **446** is heated at 90 °C in dimethylsulfoxide (DMSO)-d_6, pentacycle **447** is formed in good yield (equation 38).[233] The location of the deuterium atoms in the product indicates that the Bergman cyclization is probably followed by radical cyclization onto the tethered aromatic ring, 1,5-hydrogen atom abstraction, abstraction of deuterium from the solvent, and hydrogen elimination.



(38)

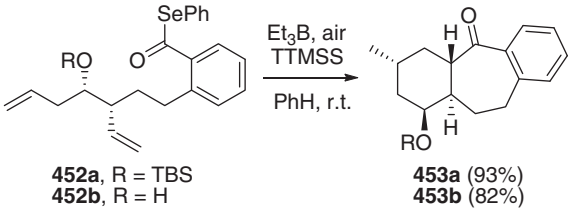
4.13.6.2 Processes Involving Acyl, Imidoyl, or Iminyl Radicals

Cyclopropyl acyl radicals and α,β-unsaturated acyl radicals rearrange to afford ketene alkyl radicals, which can participate in various cascade processes.[234] Pattenden and coworkers have taken advantage of these rearrangements to construct mono- and bicyclic ketones (**Scheme 112**).[235] The transformation of vinylcyclopropane **448** features a 6-*exo-dig* radical cyclization onto a ketene acceptor, whereas a 5-*exo-dig* cyclization occurs in the production of diquinane **451**.



Scheme 112

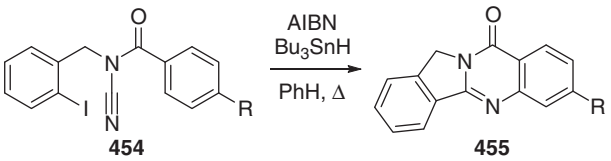
Phenyl selenoesters **452** undergo 7-*exo*/6-*exo* cyclization cascades, delivering tricyclic ketones **453** in good yield as single isomers (Scheme 113).[236] The use of TTMSS instead of the faster hydrogen atom donor Bu_3SnH is key to the success of these reactions. The stereochemistry observed in the products is consistent with both cyclizations proceeding via chair-like or pseudochair-like transition states.



Scheme 113

Malacria and coworkers have studied *N*-acyl cyanamides as radical acceptors. Tandem cyclizations of cyanamides **454** occur in good yields with both electron-withdrawing and electron-donating substituents on the arene acceptor (Table 18).[237] Calculations support a 6-*endo*-*trig* mechanism for the second cyclization rather than an *ipso* substitution followed by rearrangement.[237b] This method has been used to synthesize luotonin A,[237] and a similar route to this natural product involving radical cyclization onto a nitrile has been reported by Bowman and coworkers.[238] An unprecedented radical migration takes place during the cyclizations of vinyl iodides **456** (Table 19).[239] Migrations of alkyl groups, including the trifluoromethyl group, as well as hydrogen atom migrations are facile. Mechanistic studies support an intermolecular pathway for the migration. Related cyclizations of *N*-centered radicals derived from azides onto *N*-acyl cyanamides furnish polycyclic guanidines (equation 39).[240]

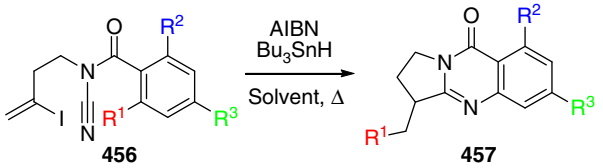
Table 18 Tandem radical cyclizations of cyanamides



454 **455**

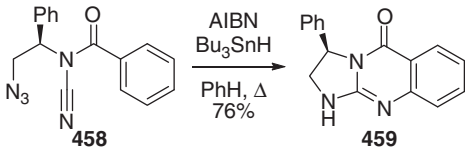
Entry	*R*	*Yield (%)*
1	H	71
2	CF_3	72
3	CN	99
4	OMe	93

Table 19 Tandem radical cyclization followed by radical migration



456 **457**

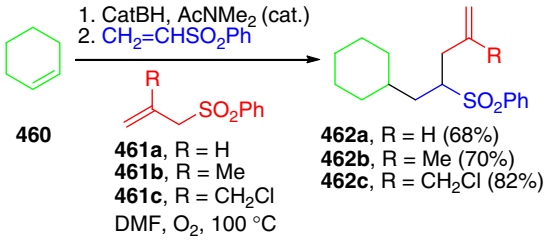
Entry	R^1	R^2	R^3	*Solvent*	*Yield (%)*
1	Me	Me	Me	PhH	47
2	Pr^i	Pr^i	Pr^i	Bu^tOH	52
3	CF_3	CF_3	H	Bu^tOH	55
4	H	Me	H	Bu^tOH	69



(39)

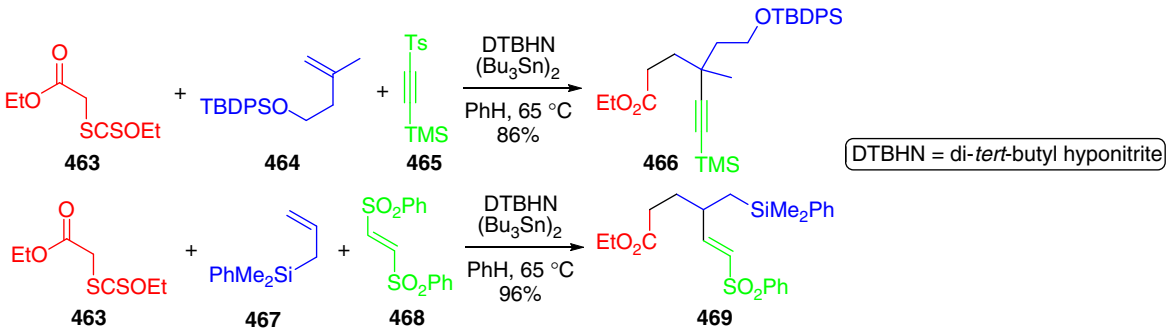
4.13.6.3 All-Intermolecular Processes

Renaud and coworkers have discovered a three-component coupling of alkenes that involves sequential intermolecular radical additions. Treatment of cyclohexene with catecholborane (CatBH) in the presence of oxygen generates the cyclohexyl radical, and this nucleophilic species adds to the electrophilic phenyl vinyl sulfone. Trapping of the resulting α-phenylsulfonyl radical with an allyl sulfone delivers the three-component coupling adducts (Scheme 114).[241]



Scheme 114

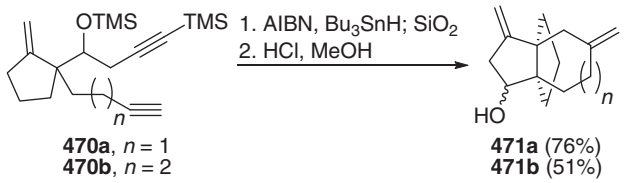
Another intermolecular three-component radical coupling has been reported by Landais and coworkers. Treatment of xanthate **463**, alkene **464**, and alkynyl sulfone **465** with hexabutylditin and di-*tert*-butylhyponitrite (DTBHN) affords alkyne **466** (Scheme 115).[242] Similarly, reaction of xanthate **463** with allylsilane **467** and vinyl *bis*-phenylsulfone **468** delivers alkene **469**. This radical cascade is presumably initiated by addition of the electrophilic radical created from the xanthate to the electron-rich alkene, followed by an addition–elimination process of the resulting radical with the alkynyl or vinyl sulfone. Careful matching of the polarity of the components is essential to controlling the reaction.



Scheme 115

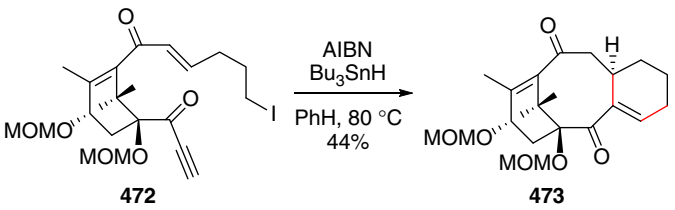
4.13.6.4 Other Noteworthy Reactions

Propellanes (e.g., **471**) are accessible via tin-promoted tandem cyclizations of enediynes (e.g., **470**), followed by destannylation and desilylation (Scheme 116).[243] Both six- and seven-membered rings can be created in the initial cyclization step. This methodology has been used to synthesize members of the modhephene family of natural products.[244]



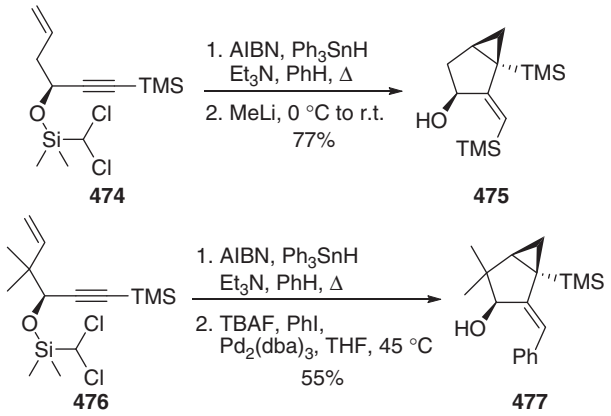
Scheme 116

Inspired by the structure of taxol, Pattenden and coworkers developed a tandem radical macrocyclization–transannular cyclization of ynone **472** (equation 40).[245] Similar processes can be used to access steroid-like compounds and other polycyclic carbocycles.[246]



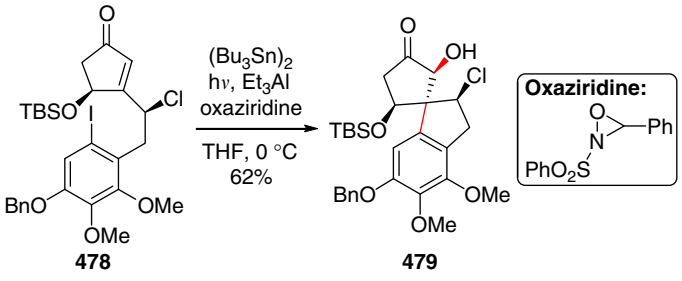
(40)

The (dichloromethyl)dimethylsilyl (DCDMS) ether moiety of substrate **474** serves as both the initiation and termination point of an interesting radical cascade. Exposure of this compound to AIBN and Ph_3SnH triggers a 5-*exo-dig* alkyl radical cyclization followed by a 5-*exo-trig* vinyl radical cyclization. Then, 3-*exo-trig* cyclization and subsequent β-elimination of a chlorine atom delivers a tricyclic adduct from which bicyclic cyclopropane **475** is liberated via O–Si bond cleavage (**Scheme 117**).[247] The silacycle intermediate can also engage in a Pd-catalyzed cross-coupling (e.g., **476**→**477**).



Scheme 117

A radical-polar crossover reaction is responsible for the conversion of aryl iodide **478** into spirocycle **479** (equation 41).[248] Although the mechanism of this transformation has not been elucidated, a plausible pathway involves stereoselective 5-*exo-trig* cyclization of the electron-rich aryl radical onto the electron-deficient enone, Et_3Al-mediated conversion of the resulting α-keto radical into an enolate, and stereoselective hydroxylation of the enolate. Spirocycle **479** has been used as an intermediate in the total synthesis of the alkaloid acutumine.[249]

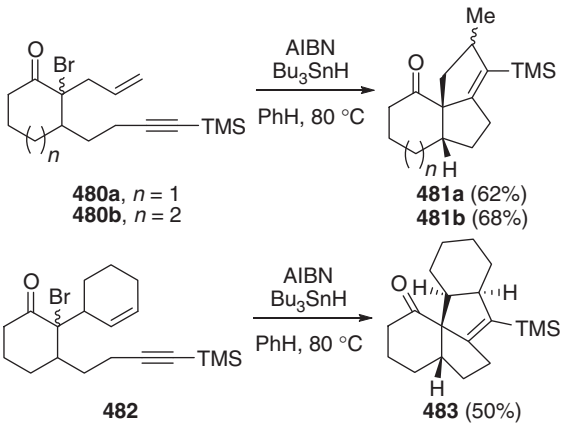


(41)

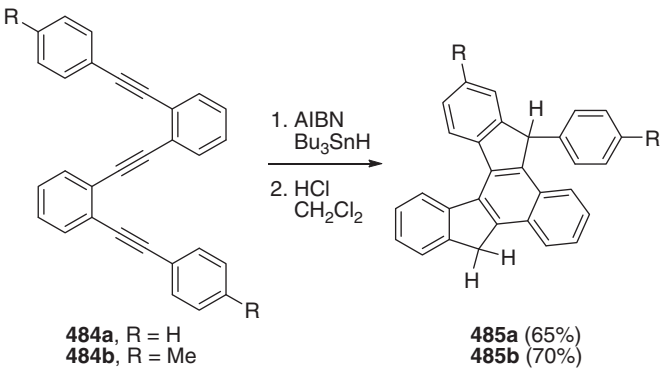
Angularly fused carbocycles **481** are available in good yield via tandem radical cyclizations of enynes **480** (**Scheme 118**).[250] Tetracyclic systems (e.g., **483**) can also be accessed by this method.

Radical cyclization cascades of aryl triynes **484** are surprisingly selective, delivering adducts **485** (**Scheme 119**).[251] The reaction proceeds by addition of the stannyl radical to the central alkyne, followed by consecutive 5-*exo-dig* and 6-*exo-dig* cyclizations onto the other alkynes. A 5-*exo-trig* cyclization onto an aromatic ring followed by a 1,5-hydrogen atom shift is believed to complete the process. A substrate with electron-donating *p*-OMe groups gives a complex mixture of products, presumably due to a lack of regioselectivity in the stannyl radical addition. This transformation could be useful for the construction of novel graphite ribbons.

On exposure to AIBN and Ph_3SnH, bis-vinyl ethers **486** undergo tandem 6-*endo*/5-*exo* radical cyclizations, furnishing bicycles **487** (**Table 20**).[252] The substrates are constructed by iterative protocols from simple building blocks. The use of a trisubstituted



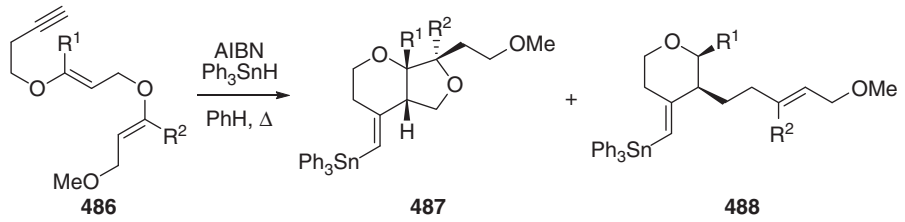
Scheme 118



Scheme 119

vinyl ether as the terminal acceptor disfavors the second cyclization, presumably due to an increased steric congestion in the transition state (entries 3 and 4).

Table 20 Tandem cyclizations onto vinyl ether acceptors



Entry	*R^1*	*R^2*	*Yield (dr)*	
			487	***488***
1	Me	H	77% (4:1)	–
2	CF_3	H	65% (7:1)	–
3	Me	Me	55% (5:1)	27% (3:1)
4	Ph	Me	–	72% (12:1)

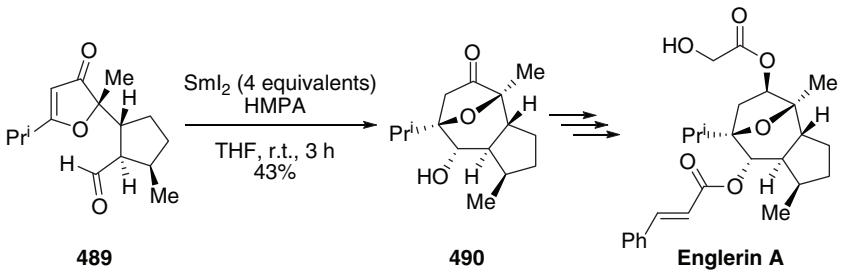
4.13.7 Notable Examples of Radical Cyclizations in Total Synthesis

Radical cyclizations are prominently featured in numerous total synthesis endeavors. The ability to form several bonds and stereocenters selectively enables complex intermediates to be fashioned from simple precursors in a single step, thereby

streamlining synthetic routes. Moreover, the mild conditions characteristic of most radical cyclizations provide a large degree of functional group tolerance, permitting implementation at the late stages of synthetic schemes. In this section, noteworthy examples of radical cyclizations in total synthesis are discussed. These examples are categorized according to the overall organizational framework of the chapter.

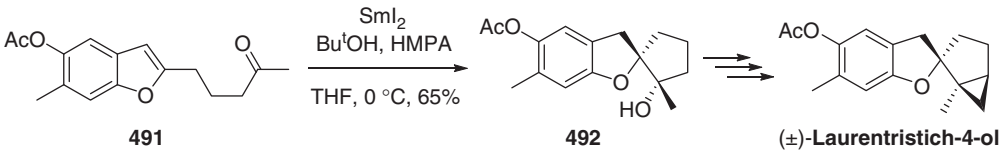
4.13.7.1 Tin-Free Cyclizations of Carbon-Centered Radicals

The explosion of new tin-free radical methods in recent years has had a profound impact on the practice of total synthesis. Thus, it is now easier than ever for practitioners of complex molecule synthesis to enjoy the benefits of radical cyclizations without experiencing the disadvantages of working with tin compounds. For example, SmI_2-mediated transformations have been used extensively in total synthesis.[16b] Additives are often essential to ensure that the desired transformation takes place, as highlighted in the total synthesis of (–)-englerin A by Chain and coworkers. HMPA was a necessary additive in the ketyl radical cyclization of aldehyde **489** (Scheme 120).[253] The use of LiCl led to a pinacol-type coupling, whereas protic additives resulted in reduction of the aldehyde. Another SmI_2–HMPA-mediated ketyl radical cyclization is found in the total synthesis of (±)-laurentristich-4-ol by Wang, Li, and coworkers (Scheme 121).[254]



489 **490** **Englerin A**

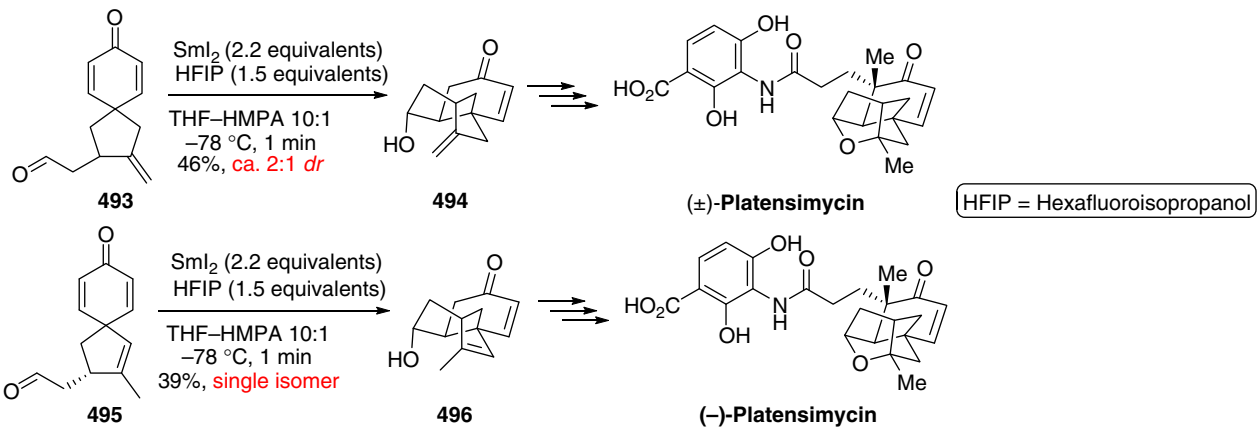
Scheme 120



491 **492** **(±)-Laurentristich-4-ol**

Scheme 121

The impact of subtle structural features on the stereoselectivity of radical cyclizations is manifest in the total synthesis of platensimycin by Nicolaou and coworkers. In the course of a racemic synthesis, 6-*exo* ketyl radical cyclization of aldehyde **493** provided tricycle **494** in modest (2:1) *dr* (Scheme 122).[255] In contrast, during the subsequent enantioselective synthesis it was discovered that simply shifting an alkene from an exocyclic to an endocyclic orientation resulted in a completely diastereoselective reaction (i.e., **495** → **496**).[256]

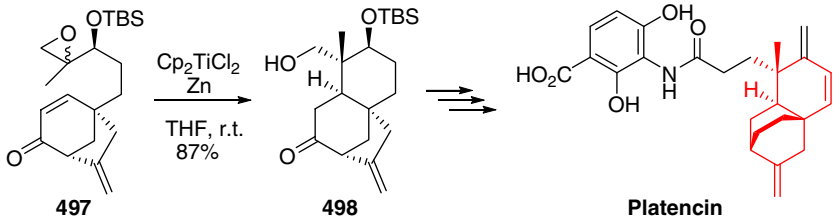


493 **494** **(±)-Platensimycin**

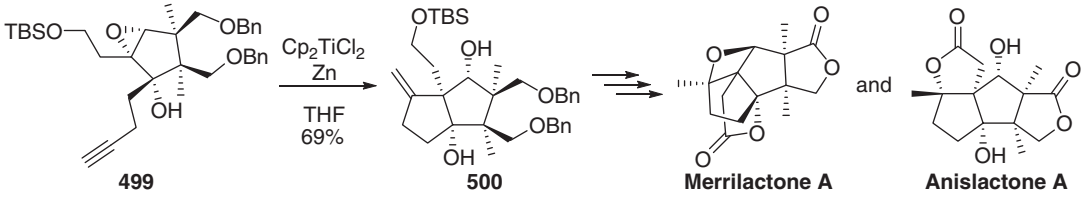
495 **496** **(–)-Platensimycin**

Scheme 122

In the total synthesis of platencin, Yoshimitsu and coworkers employed epoxide **497** in a 6-*exo* radical cyclization using stoichiometric Cp_2TiCl generated *in situ* (Scheme 123).[257] The stereoselectivity is attributed to cyclization via a chair-like transition state with the silyl ether and titanoxymethyl groups in equatorial positions. A subsequent radical skeletal rearrangement was key in delivering the natural product. Another example of using a Ti(III)-mediated radical cyclization to forge a quaternary carbon stereocenter can be found in the syntheses of (±)-merrilactone A and (±)-anislactone A by Greaney and coworkers (Scheme 124).[258] Dilute conditions combined with slow addition of the Ti(III) reagent to the epoxide were both crucial to the success of this reaction.

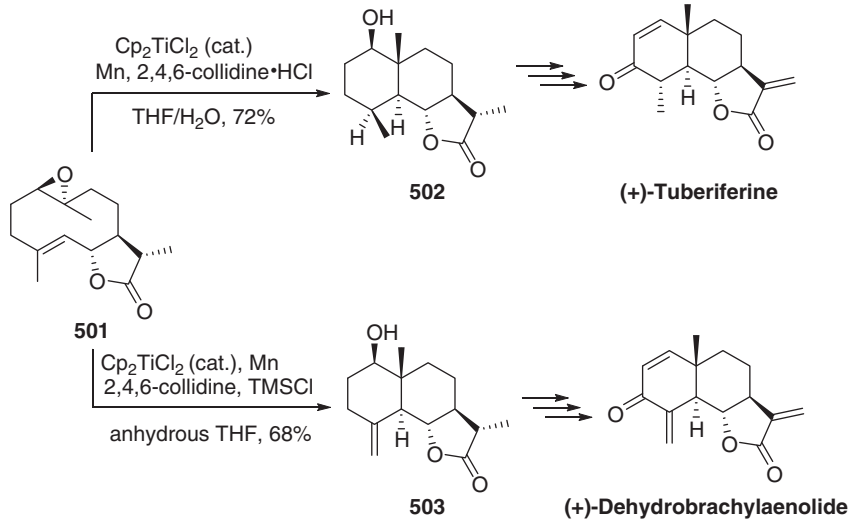


Scheme 123



Scheme 124

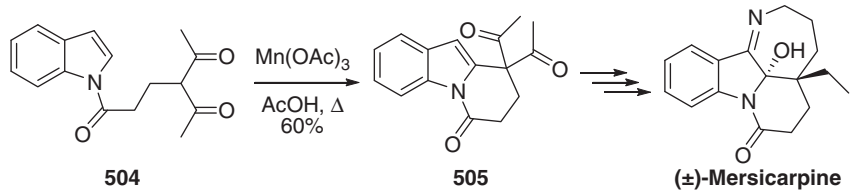
Oltra and coworkers used a divergent strategy featuring Ti(III)-catalyzed cyclizations to synthesize epoxygermacrolides. In a THF/H_2O mixture, epoxide **501** gave rise to tricyclic lactone **502**, the precursor for (+)-tuberiferine. In contrast, alkene **503** was produced under anhydrous conditions and subsequently converted into (+)-dehydrobrachylaenolide (Scheme 125).[259] When water is present, the tricyclic radical is reduced by a Ti(III) aqua complex, whereas in the absence of water a mixed disproportionation yields the alkene.



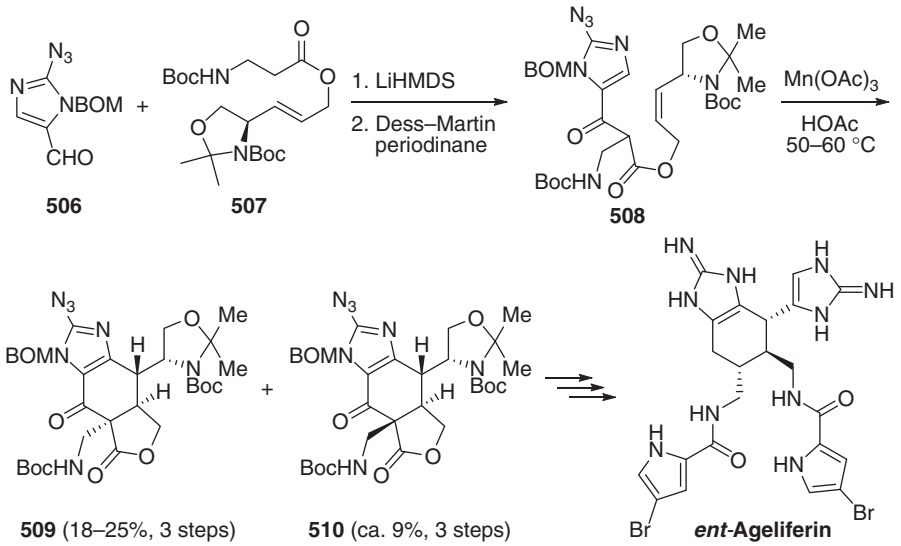
Scheme 125

Kerr and coworkers utilized methodology previously developed in their laboratory[73] to accomplish the total synthesis of mersicarpine. Treatment of 1,3-diketone **504** with $Mn(OAc)_3$ delivered tricyclic amide **505** as the result of an oxidative 6-*exo* radical cyclization (Scheme 126).[260] An $Mn(OAc)_3$-promoted tandem cyclization of a complex, highly functionalized substrate is

found in the total synthesis of ageliferin by Chen and coworkers. Epimeric lactones **509** and **510** were produced from β-ketoester **508** in a 2.5–3:1 ratio (Scheme 127).[261] Fortunately, both the epimers could be used to complete the total synthesis.

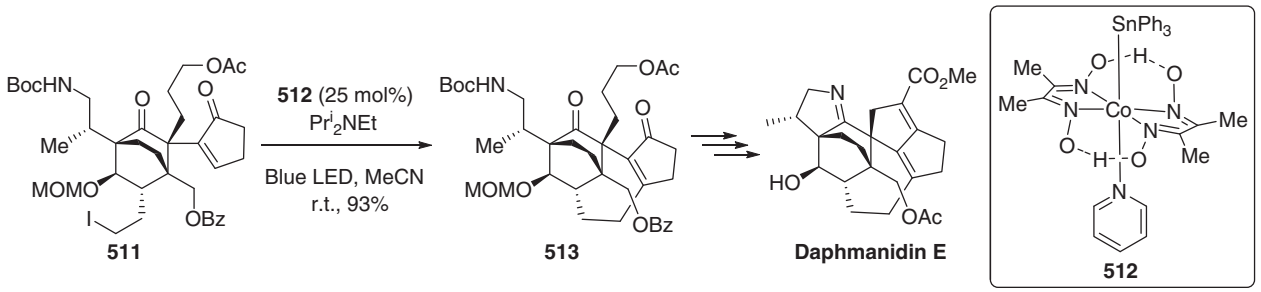


Scheme 126



Scheme 127

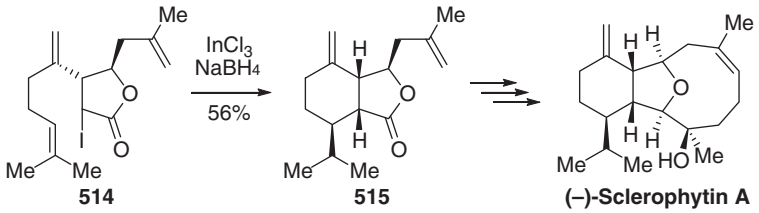
Carreira and Weiss employed their previously developed cobaloxime-catalyzed, light-promoted alkyl Heck-type cyclization[95] in the total synthesis of daphmanidin E (Scheme 128).[262] The excellent yield observed in a 7-*endo* cyclization of a highly congested species is quite noteworthy.



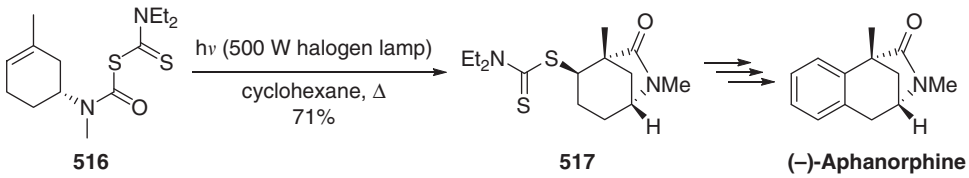
Scheme 128

Morken and coworkers implemented the $InCl_3$–$NaBH_4$ conditions introduced by Baba[77] to accomplish a 6-*exo* radical cyclization in the synthesis of (–)-sclerophytin A (Scheme 129).[263] The reaction proceeded with excellent stereoselectivity ($>10{:}1$ *dr*), presumably as the result of a chair-like transition state. A tin-promoted cyclization of iodide **514** proceeded with comparable efficiency.

A metal-free photoinitiated group-transfer radical cyclization was used by Grainger and Welsh in the total synthesis of (–)-aphanorphine. Irradiation of dithiocarbamate **516** with a 500 W halogen lamp produced a carbamoyl radical, which then cyclized to afford bridged adduct **517** as a single diastereomer after group transfer to the less-hindered convex face (Scheme 130).[264]

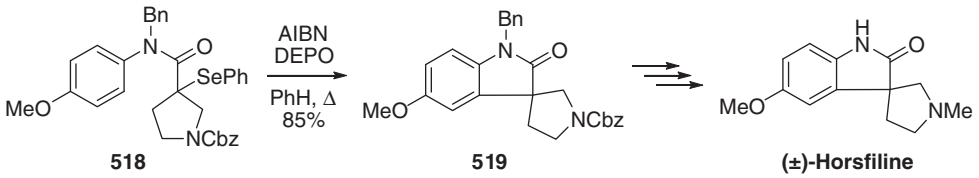


Scheme 129

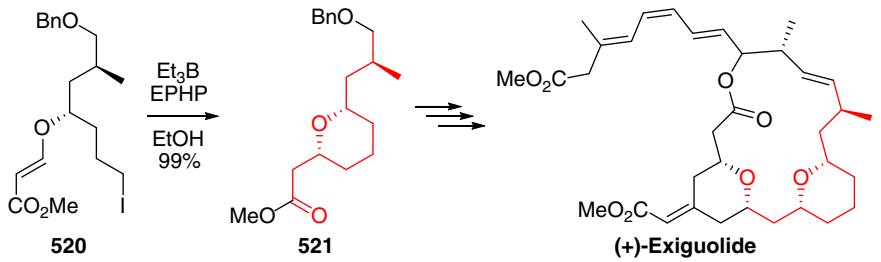


Scheme 130

In the course of a formal synthesis of horsfiline, Murphy and coworkers used the phosphorus radical precursor diethylphosphine oxide (DEPO)[265] to perform the cyclization of phenylselenide **518** (Scheme 131).[266] DEPO is a slower hydrogen atom donor than Bu_3SnH, and is thus useful in reactions where premature reduction would be problematic. Another example of a phosphorus-based radical cyclization is found in the synthesis of (+)-exiguolide by Lee and coworkers. When β-alkoxyacrylate **520** was treated with ethylpiperidine hypophosphite (EPHP) and Et_3B, a quantitative conversion to oxane **521** was achieved with complete diastereoselectivity (Scheme 132).[267]



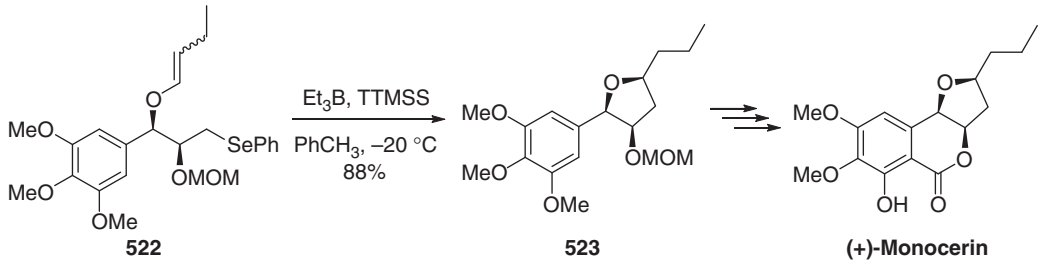
Scheme 131



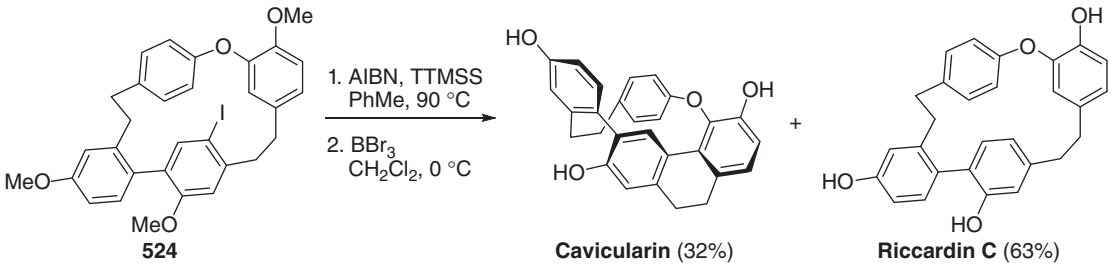
Scheme 132

TTMSS, like DEPO and EPHP, is a commonly used alternative to tin hydrides. In the synthesis of (+)-monocerin, Lee and coworkers used TTMSS with Et_3B as the initiator to mediate the 5-*exo*-*trig* cyclization of vinyl ether **522** (Scheme 133).[268] This example is notable, as simple vinyl ethers are utilized much less frequently as radical acceptors than their β-alkoxyacrylate counterparts (cf. Scheme 132). In the penultimate step of the total synthesis of cavicularin, Harrowven and coworkers employed TTMSS in the transannular radical cyclization of aryl iodide **524**. The desired natural product was formed in 32% yield after demethylation, an impressive result given the highly strained nature of the ring system (Scheme 134).[269] The major product was derived from iodide reduction, but this species could also be converted into a natural product, riccardin C. Interestingly, treatment of the aryl bromide corresponding to **524** with Bu_3SnH instead of TTMSS increased the bias toward the uncyclized, reduced product.[270]

Chatgilialoglu and coworkers developed an interesting tin-free approach to the synthesis of cyclonucleosides. Treatment of aldehyde **525** with TTMSS and AIBN triggered silyl radical addition to the aldehyde oxygen, producing an α-silyloxy radical.

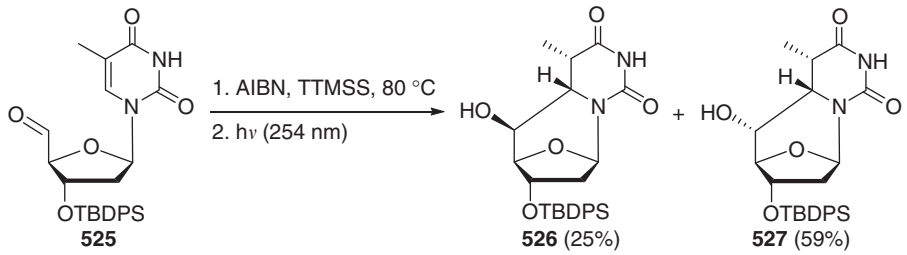


Scheme 133



Scheme 134

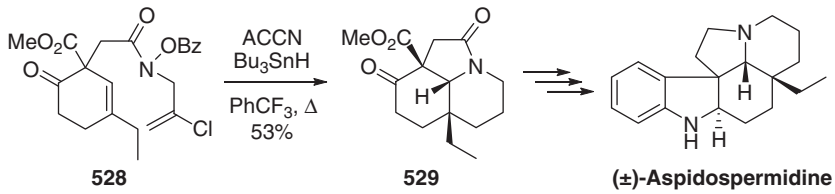
This species then cyclized onto the neighboring thymine moiety, giving a 3:7 mixture of diastereomeric TTMSS ethers. Irradiation of this mixture with ultraviolet (UV) light cleaved the silyl ethers, affording alcohols **526** and **527** (Scheme 135).[271]



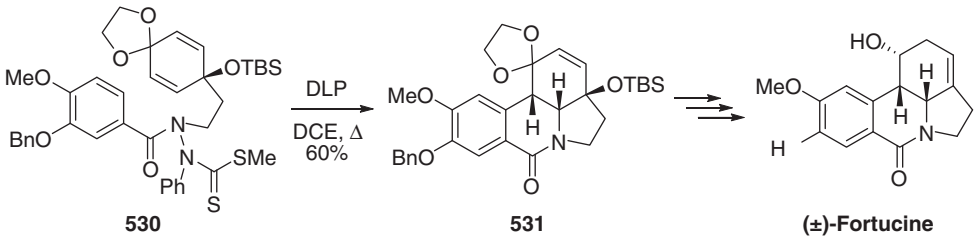
Scheme 135

4.13.7.2 Cyclizations Involving Heteroatom-Based Radicals or Acceptors

In the synthesis of (±)-aspidospermidine, Zard and coworkers implemented a tandem cyclization initiated by a nitrogen-centered radical. Exposure of *N*-benzoate **528** to ACCN and Bu_3SnH delivered tricycle **529** by means of a 5-*exo*/6-*endo* cyclization (Scheme 136).[272] Minor amounts (29%) of a monocyclized compound were also obtained. The chlorine atom, which was cleaved by excess Bu_3SnH after cyclization was complete, was essential for controlling the regioselectivity of the second cyclization. A related strategy was used in the total synthesis of (±)-13-deoxyserratine.[272b] A different amidyl radical precursor was utilized in the synthesis of (±)-fortucine. Substrate **530** was refluxed with DLP to afford highly functionalized *cis*-fused pentacycle **531** (Scheme 137).[273] The desired regioisomer (i.e., cyclization *para* with respect to the benzyloxy group) was favored by a 14:1 ratio.

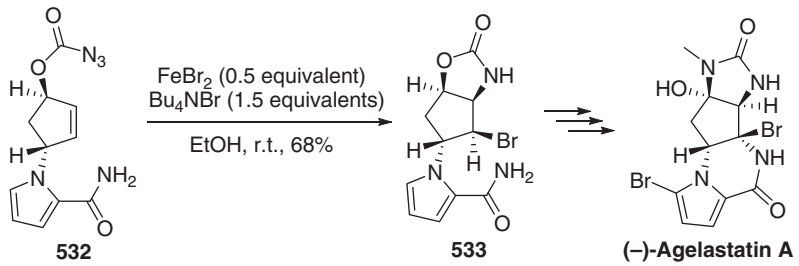


Scheme 136



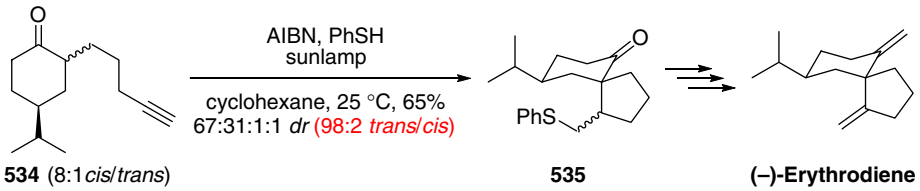
Scheme 137

A radical aminobromination functioned as a key step in the total synthesis of agelastatin A by Yoshimitsu, Tanaka, and coworkers. Azidoformate **532** was treated with substoichiometric amounts of $FeBr_2$ to generate a nitrogen-centered radical, which cyclized onto the proximal face of the alkene. A bromine atom was then transferred from the *N*-bound iron atom to the carbon-centered radical, resulting in a net *syn* addition (Scheme 138).[274] Regeneration of $FeBr_2$ by Bu_4NBr permitted the use of substoichiometric quantities of the iron salt.



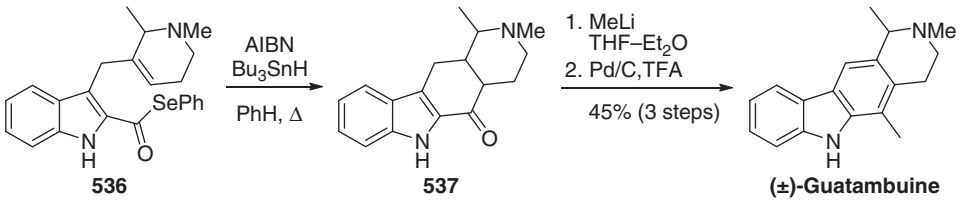
Scheme 138

A cyclization triggered by phenylthiyl radical addition to an alkyne was featured in the synthesis of (–)-erythrodiene by Renaud and coworkers. The vinyl radical formed by the aforementioned addition to alkyne **534** underwent 1,5-hydrogen atom abstraction followed by highly *trans*-selective 5-*exo*-*trig* cyclization, producing spirocycle **535** as an inconsequential mixture of diastereomers (Scheme 139).[275] The use of a nonpolar solvent at room temperature was crucial to obtaining high diastereoselectivity in the cyclization step.

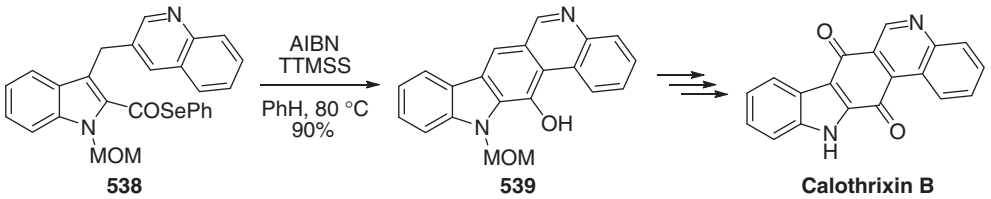


Scheme 139

Bennasar and coworkers employed an acyl radical cyclization in the total synthesis of guatambuine (Scheme 140).[276] The lack of stereoselectivity was inconsequential, as the newly formed stereocenters were destroyed on subsequent aromatization. The acyl radical cyclization of quinoline **538**, a key step in the total synthesis of calothrixin B, was accomplished with AIBN and TTMSS (Scheme 141).[277] The *N*-methoxymethyl (*N*-MOM) group was essential, as cyclization of the *N*-methyl congener of **538** yielded overoxidized products derived from the reaction of the cyclic radical intermediate with AIBN.

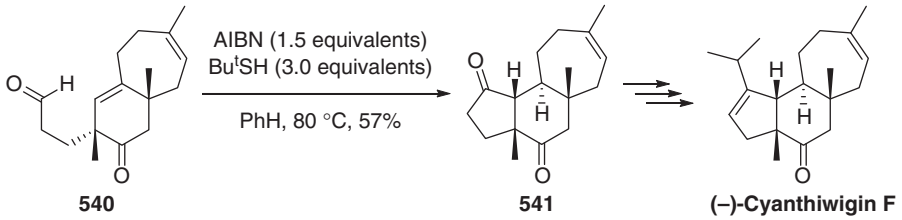


Scheme 140



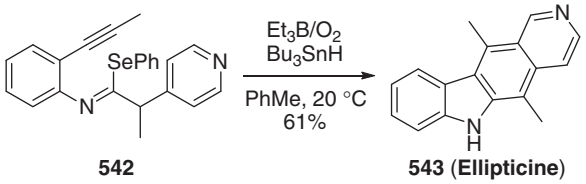
Scheme 141

Stoltz and Enquist applied Tomioka's thiol-mediated protocol for generating acyl radicals[151] to the total synthesis of (–)-cyanthiwigin F (**Scheme 142**).[278] The *cis*, *anti*, *trans* stereochemistry of the natural product was installed with complete selectivity in this step.

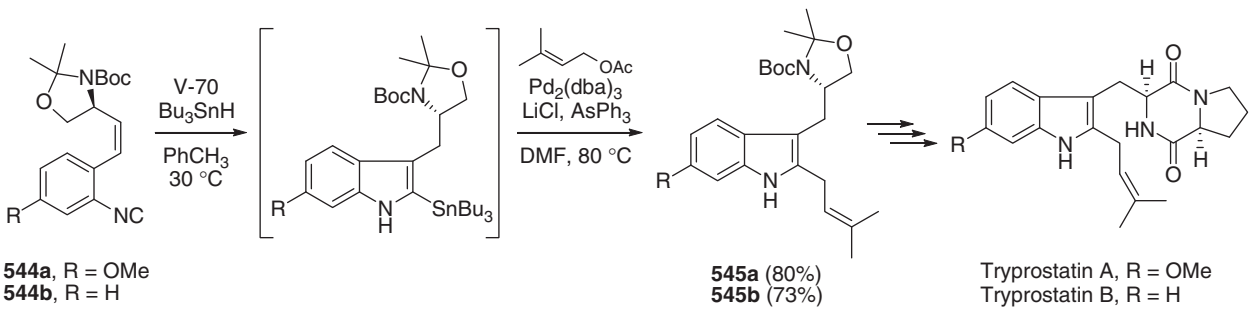


Scheme 142

In the final step of the synthesis of ellipticine, Bowman and coworkers performed an imidoyl-radical-initiated tandem cyclization with phenylselenide **542** (equation 42).[279] The initial ring closure occurred in a 5-*exo-dig* fashion, and it is believed that an *ipso* cyclization followed by a neophyl rearrangement and rearomatization delivered the final product. In another example of an imidoyl radical cyclization, Fukuyama and coworkers developed a one-pot Fukuyama indole synthesis[158] – π-allyl Stille coupling protocol to enable the construction of tryprostatins A and B (**Scheme 143**).[280]

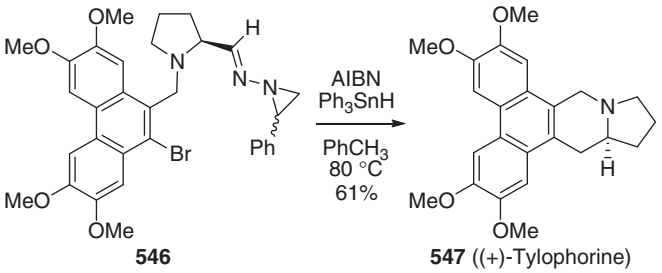


(42)



Scheme 143

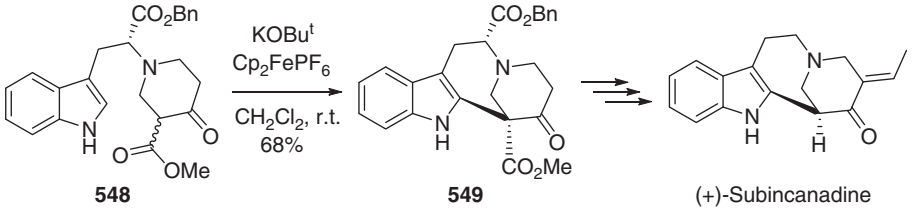
In the final step of the total synthesis of tylophorine, Stoye and Opatz took advantage of the methodology developed by Kim and coworkers[281] by employing the *N*-aziridinyl imine group as a radical acceptor. A 6-*exo-trig* cyclization of the aryl radical derived from bromide **546** yielded a nitrogen-centered radical, which underwent successive fragmentations to furnish the natural product along with N_2 and styrene (equation 43).[282]



(43)

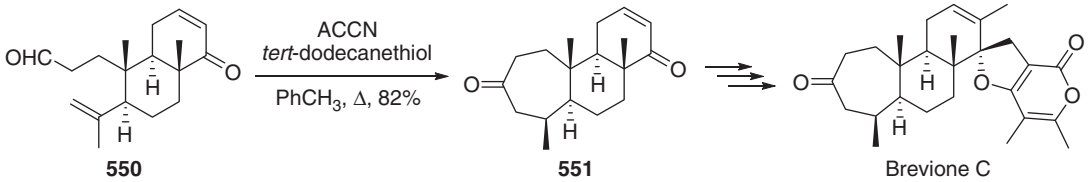
4.13.7.3 Cyclizations That Form Unusual-Sized Rings

In the course of synthesizing subincanadine F, Li and coworkers accomplished an unusual 7-*endo-trig* cyclization. Oxidative cyclization of *β*-keto ester **548** was unsuccessful with reagents such as CAN, $Mn(OAc)_3$, $Cu(OAc)_2$, and $FeCl_3$. Fortunately, oxidation of the derived enolate with Cp_2FePF_6 enabled the desired cyclization to proceed (**Scheme 144**).[283] The preference for 7-*endo-trig* cyclization can be attributed to the formation of a stabilized benzylic radical.



Scheme 144

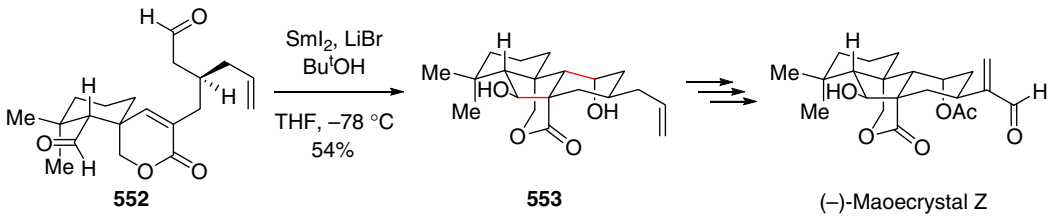
Shishido and coworkers applied Tomioka's thiol-mediated acyl radical generation method[152] to a 7-*endo* cyclization in the total synthesis of brevione C (**Scheme 145**).[284] The chemoselectivity of this reaction (i.e., no cyclization onto the enone moiety) is noteworthy.



Scheme 145

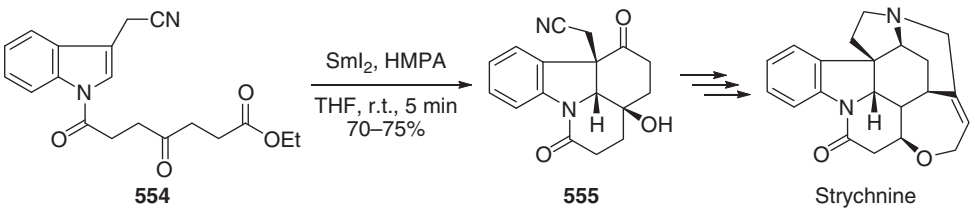
4.13.7.4 Sequential Radical Reactions

Numerous examples of tandem or cascade radical reactions in total synthesis have appeared in the recent literature. Reisman and coworkers implemented a SmI_2-mediated ketyl radical cyclization–intramolecular aldol cascade at a late stage in the total synthesis of (–)-maoecrystal Z (**Scheme 146**).[285] Two rings and four stereocenters were created in this reaction, and the process occurred with excellent chemo- and stereoselectivity. During a formal total synthesis of strychnine, Beemelmanns and Reissig[286] performed an SmI_2-promoted tandem cyclization with ketone **554** (**Scheme 147**). Presumably, 6-*exo* ketyl radical cyclization was



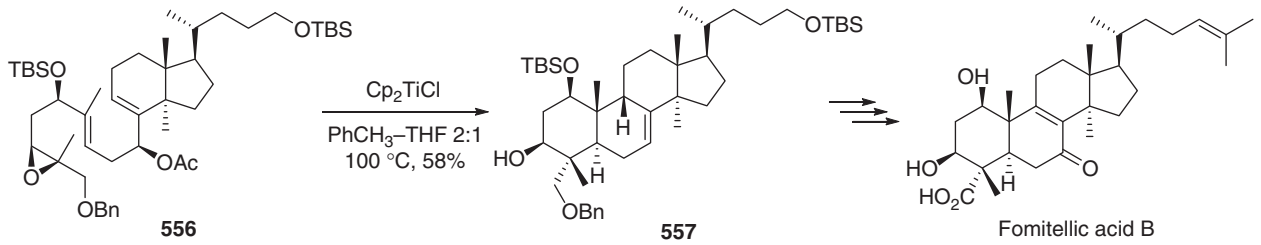
Scheme 146

followed by intramolecular acylation of the resulting organosamarium intermediate. In addition to forming two rings, this transformation generated three stereocenters with the correct relative configuration.



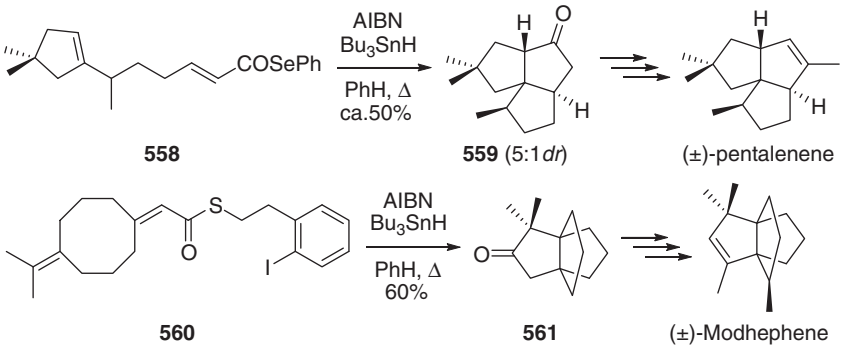
Scheme 147

Kobayashi and coworkers used a Ti(III)-mediated tandem radical cyclization of epoxide **556** to fashion the steroid ring system of fomitellic acid B (**Scheme 148**).[287] Interestingly, the epimeric acetate did not undergo the second cyclization. It is believed that destabilizing nonbonding interactions between the acetate and the neighboring methyl group in the transition state were responsible for this unexpected phenomenon.



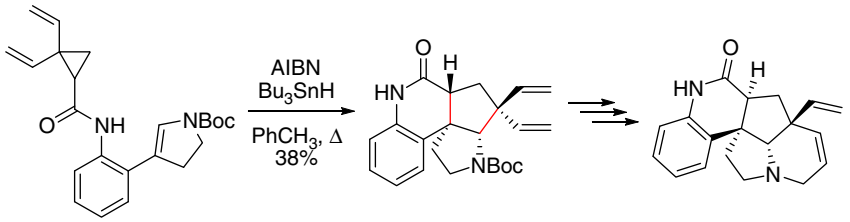
Scheme 148

Pattenden and coworkers exploited two tandem radical cyclizations in the synthesis of triquinane natural products. Treatment of α,β-unsaturated phenylselenoester **558** with AIBN and Bu_3SnH delivered tricyclic ketone **559**, which was used as an intermediate in the synthesis of pentalenene (**Scheme 149**).[288] The process is believed to proceed via initial α,β-unsaturated acyl radical formation and subsequent 5-*exo-trig* cyclization of the α-ketenyl alkyl radical resonance structure. A final 5-*exo-dig* cyclization onto the ketene and hydrogen atom abstraction completes the reaction. A related transformation involving consecutive 5-*exo-trig* cyclizations of 2-(*o*-iodophenyl)ethyl thioester **560** furnished propellane **561**, an intermediate in the synthesis of modhephene.



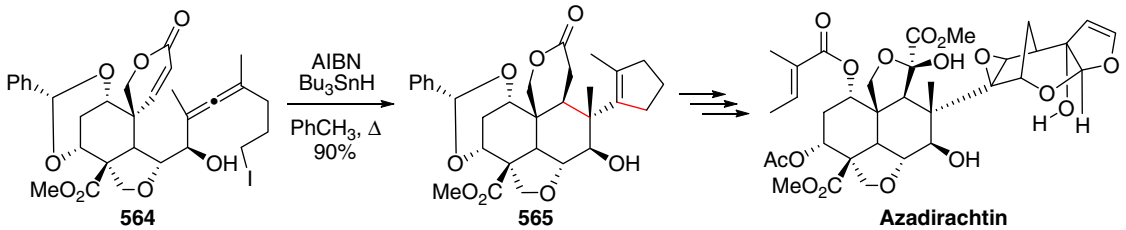
Scheme 149

Curran and Zhang[289] implemented an unusual tandem radical cyclization in the synthesis of epimeloscine and meloscine. Divinylcyclopropane **562** was treated with AIBN and Bu_3SnH to deliver tetracycle **563** in 38% yield (**Scheme 150**). The corresponding *N*-benzyl amide substrate cyclized in 55% yield, but debenzylation proved unsuccessful. Presumably, the reaction pathway involves tributyltin radical addition to a vinyl group, cyclopropane ring opening, 6-*exo* cyclization of the electron-deficient α-carbonyl radical onto the electron-rich enamide, and 5-*exo* cyclization onto the allyltin moiety with expulsion of the tributyltin radical.



Scheme 150

Inspired by a radical cyclization involving an allene acceptor that was developed by Ley for the total synthesis of azadiractin,[290] Watanabe and coworkers performed the stereoselective tandem radical cyclization of allene **564** as part of an approach to the same target molecule (**Scheme 151**).[291] The use of a lactone as the acceptor for the second cyclization proved crucial, as cyclization of a related substrate possessing an acyclic enoate proceeded in low yield.



Scheme 151

4.13.8 Conclusions

Radical cyclizations and sequential radical reactions continue to provide fertile areas for the discovery of new and useful synthetic transformations. In particular, the number of recently developed tin-free radical reactions is truly remarkable. Moreover, creatively designed radical cascades enable the construction of complex products from relatively simple starting materials, often in a highly stereoselective fashion. The widespread use of radical cyclizations in total synthesis demonstrates the value of these methods for preparing sterically hindered products that contain multiple functional groups. As the pace of discovery shows no signs of slowing, radical cyclizations and sequential radical reactions are likely to maintain their prominent positions in the field of organic synthesis.

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4.14 Vinyl Substitutions with Organopalladium Intermediates

EM Butler, R Doran, CM Wilson, and PJ Guiry, University College Dublin, Dublin, Ireland

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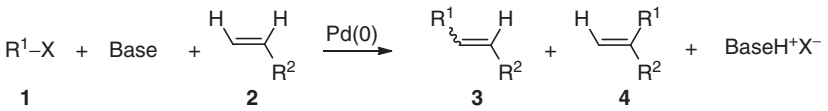
4.14.1 Introduction

The Heck reaction is the vinylation of aryl/vinyl halides or triflates in the presence of a base and catalyzed by Pd(0) complexes, resulting in the formation of a C–C bond (equation 1).[1] Its recent exploitation in the key steps of many total syntheses of natural products[2] has been due to a better understanding of the proper choice of reactants, solvents, bases, additives, catalyst precursors, and ligands necessary for optimal reaction conditions.



(1)

R^1 : aryl, alkenyl
R^2 : aryl, alkenyl, alkyl, OR, CO_2R...
X = I, Br, OTf, N_2^+...

4.14.2 Catalyst Development

Over the past 40 years, vinyl substitution with organopalladium intermediates – the Heck reaction – has developed into one of the most powerful transformations in organic synthesis. From the traditional Heck couplings carried out with aryl/vinyl iodides/bromides has emerged the possibility to utilize organo-triflates, carbonyl/sulfonyl chlorides, diazonium, and iodonium salts as the electrophilic coupling partner.[3] Catalytic systems have been developed to allow processing of less reactive substrates such as aryl chlorides (Section 4.14.2.8) and electron-rich alkenes and also control the regioselectivity (Section 4.14.3) of the reaction and prevent doublebond migration. For the purpose of this section, the development of different catalytic systems for the coupling of aryl halides with alkenes will be the sole focus as this is by far the most prevalent Heck reaction.

The first step (**A**) in the commonly accepted catalytic cycle is the oxidative addition of an aryl/alkenyl halide or pseudohalide (X=OTf, OMs...) to Pd(0)L_2 affording the Pd(II)L_2 complex **5** (**A**). The rate of the oxidative addition is sensitive to the nature of alkenyl/aryl halide or pseudohalide and the order of reactivity has been experimentally determined to be I > OTf > Br > Cl.[4] In the second step (**B**), the coordination of the Pd(II) complex **5** to the double bond of the alkene leads to the formation of π-complexes. Depending on the reaction conditions, the mechanism involves the dissociation of either a halide (cationic route via **6**) or one ligand donor atom (neutral route via **7**) to allow the coordination of the olefin.[5] The π-cationic complex **6** is generally generated by using an aryl or alkenyl triflate (the Pd-OTf is easily dissociated due to the weakness of the bond[6]) or an aryl/alkenyl halide in the presence of a halide scavenger (Ag^+,[7] Tl^+,[8] or K^+ in aqueous dimethylformamide (DMF)[9]). The π-neutral pathway is the predominant route starting from aryl/alkenyl halide or triflates in the presence of an excess of halide anion which leads to a nucleophilic displacement of the triflate.[10] Then, the *syn*-insertion of the alkene into the π-complexes occurs providing linear (**8** or **10**) and/or branched (**9** or **11**) σ-alkyl Pd(II) complexes. The R^1 group will either add to the α-carbon of the alkene yielding branched products (**9** or **11**) or to the β-carbon (**8** or **10**) providing linear complexes. The regioselective outcome of this process depends on various factors such as the nature of R^2, ligand, or reaction conditions. In the last step (**C**), a *syn*-β-hydrogen elimination gives rise to the Heck products (**12** and/or **13**) and a hydridopalladium complex, from which the catalytically active Pd(0) complex is regenerated after reductive elimination by a base.

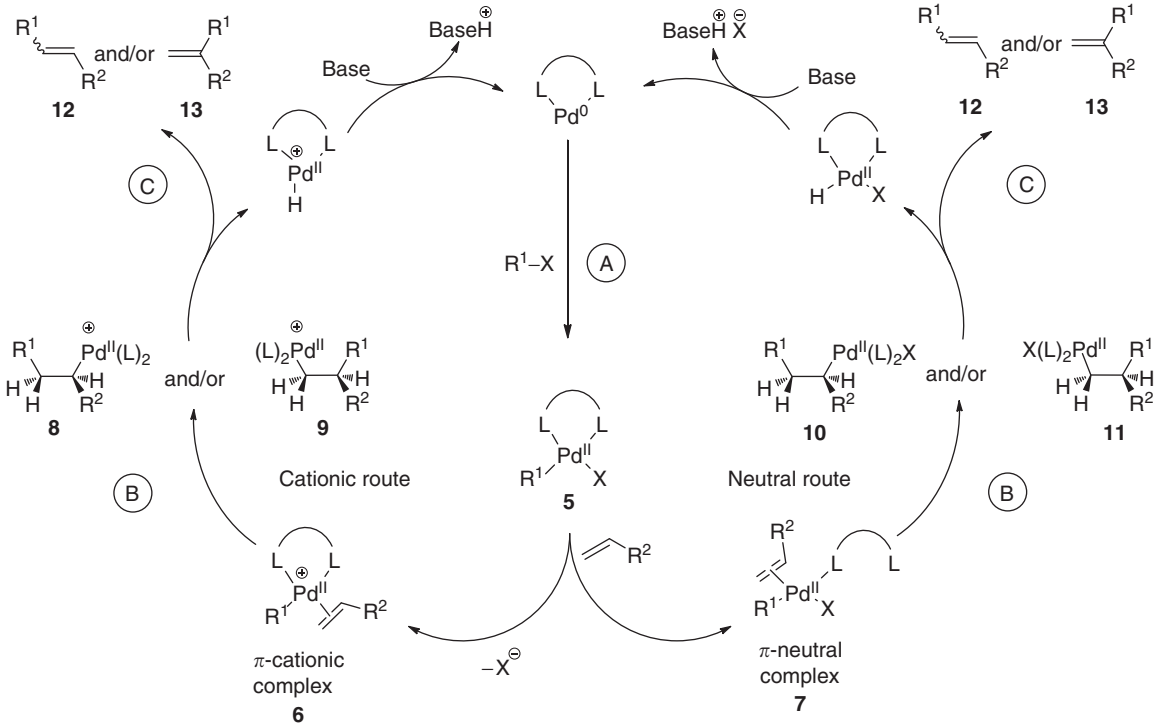
It is important to note from the outset that there are considerable differences between the Heck reaction and other Pd-catalyzed cross-coupling reactions due to fundamentally different reaction mechanisms. Both are initiated by the same oxidative addition step described above and as a result have the same Pd(II) intermediate. However, in other Pd cross-coupling reactions a strong nucleophile can substitute a halide in the coordination sphere whereas this is not possible in the Heck reaction as shown in Scheme 1. In cross-coupling reactions, either two monodentate ligands or one bidentate ligand remain in the coordination sphere allowing control of the catalyst by variation of these ligands. In the Heck reaction via the neutral path only a single stable ligand remains in the coordination sphere and monodentate ligands prefer to form diligated complexes whereas via the cationic pathway all of the ancillary ligands are labile/hemilabile giving an undefined coordination sphere around Pd. As a result it is difficult to control the Heck reaction by variation of the ancillary ligands unlike most other transition metal-catalyzed processes. Therefore, all the components involved in the reaction must be considered to improve the catalytic activity.

4.14.2.1 Catalytic Systems

There are four types of catalytic systems that have been identified and classified by Beletskaya and Cheprakov, based on substrate scope, dependence on ancillary ligands, catalytic efficiency, and on specific conditions.[11]

4.14.2.1.1 Type 1 catalytic system

The type 1 catalytic system could be considered the classical Heck reaction which requires substrates, such as aryl iodides/activated aryl bromides, that are highly reactive toward oxidative addition. Any form of Pd(0) or Pd(II) can be used to generate a complex



Scheme 1

containing three labile/hemilabile ligands for catalysis to occur, with the coordination sphere of Pd undefined. There is no requirement for specific ancillary ligands and often phosphines or other strongly coordinating ligands can retard the reaction. The reactions can be carried out at temperatures between room temperature and 180 °C in polar coordinating solvents with Pd loadings of 10^{-5} to 0.1 mol%. In general, type 1 processes are high yielding, reliable, simple to scale up, and very high turnover numbers (TONs) are achievable.

4.14.2.1.2 Type 2 catalytic system

The type 2 catalytic systems were initially developed by Spencer using less reactive substrates, typically unactivated aryl bromides and activated aryl chlorides following extensive optimization of the reaction conditions using any form of Pd(0) or Pd(II).[12] These types of systems are very sensitive to the optimized conditions of solvent, base, additives, temperature, and precatalyst loading. Typical catalyst loadings range from 0.05 to 0.5 mol%. As in the type 1 systems, there is no requirement for any specific ancillary ligands. Reaction temperatures range from 120–180 °C in polar coordinating solvents. Tedicyp **14**, from the Doucet–Santelli family of tetraphosphine ligands, is a fine example of a ligand applied to type 2 systems (Figure 1). It catalyzes the Heck reaction of a number of aryl bromides with a large variety of alkenes employed including acrylates, styrene derivatives and linear and cyclic alkenes (Figure 1).[13]

Tedicyp
14

Figure 1 Tedicyp, a tetraphosphine ligand for type 2 catalytic systems.

4.14.2.1.3 Type 3 catalytic system

The type 3 system could be referred to as the Hartwig–Fu protocol which extended the substrate scope to unactivated aryl chlorides (Section 4.14.2.8).[14] These substrates cannot be readily reacted in type 1 and type 2 systems and yields are low. As a result, ligands are required to facilitate the oxidative addition step in order to increase yields and make this transformation viable. In order to achieve this, a neutral Pd complex is needed with a single ancillary ligand which will accelerate the rate of oxidative addition. If the complex has more than one ancillary ligand or other reaction components which may act as ligands it will inhibit

coordination of the alkene. The types of ancillary ligands required to speed up oxidative addition are electron-rich and bulky and generally phosphine-containing. The Pd loadings are significant, generally at least 0.5 mol%. The complexes used in type 3 systems require temperatures of up to 120 °C in order to activate the complex, whereas higher temperatures may lead to deligation and deactivation of the catalyst. The development/application of new ligand classes in this system is a highly active recent research field and will be discussed in more detail in Section 4.14.2.8.

4.14.2.1.4 Type 4 catalytic system

The type 4 catalytic system proceeds via the cationic reaction pathway. Bidentate phosphines are seldom used in nonasymmetric Heck reactions although they are very important for regio- (Section 4.14.3) and stereoselective processes (Section 4.14.8). These systems are catalyzed by a well-defined coordination sphere around Pd leading to selectivity. They require a strongly binding bidentate ligand which will remain coordinated throughout the catalytic cycle. To achieve catalysis via this route an anionic ligand must dissociate to free up a coordination site for alkene coordination and subsequent migratory insertion steps. The design of these systems is of critical importance to maintain stable conditions for a well-defined complex and to prevent bis-chelation leading to inactivity.

4.14.2.2 Substrates for Vinyl Substitution

The most important substrates for the Heck reaction are aryl halides that are subdivided into (a) very reactive, e.g., aryl iodides and electron-deficient aryl bromides; (b) moderately reactive, e.g., all other aryl bromides and electron-deficient aryl chlorides, and (c) unreactive, e.g., other aryl chlorides including electron-rich substrates. In the case of type 1 and type 2 systems (Section 4.14.2.1), where Pd has an undefined coordination sphere, the oxidative addition step does not show a large dependence on the substituent(s) on the aryl halide. However, this does not account for the large difference in reactivity between electron-rich and electron-poor halides. This difference is not observed in Heck reactions where the Pd catalyst has a defined coordination sphere with a stable ligand, where the reactivity difference between electron-rich and -poor substrates is not as pronounced. In systems with an undefined coordination sphere around Pd (most common), iodides are more reactive than bromides which are much more reactive than chlorides. However, iodides are generally not useful for processes where Pd has a definite stable ligand (type 3, Section 4.14.2.1.3) due to iodide itself being a strongly bound ligand whereas chloride is much more labile. Hence, the catalyst is less stable and more prone to deactivation when aryl chlorides are used, resulting in lower yields.

4.14.2.3 Ligands on Pd

There is a huge variety of ancillary ligands used for the Heck reaction and it is generally accepted that phosphines have a distinct effect. The initial seminal reports by Heck described phosphine-free conditions for vinylations of aryl iodides and the use of PPh_3 or P(*o*-tolyl)$_3$ for aryl bromides.[1b,15] However, it is not sufficient to simply classify the ligands into phosphine-containing and phosphine-free categories. The different types of ligands have different functions in the Heck reaction. The first is the support of Pd(0) as a reactive monomeric species and prevention of Pd black formation. This function can be provided by simple labile/hemilabile monodentate phosphine ligands or by nonphosphine ligands such as bases, anions, or even coordinating solvents. The second is the strongly binding mono-, di-, or tridentate ligands which coordinate Pd into a relatively stable complex and thus function as a slow-release catalyst which slowly releases the active Pd(0) species by thermal decomposition or activation by other reaction components. A third function of ancillary ligands is to increase the rate of oxidative addition for unreactive substrates, such as electron-rich aryl chlorides. This can be achieved by the use of bulky monodentate electron-rich ligands (generally phosphines). The final possible function of ancillary ligands is to form a stable coordination sphere by using stable bidentate ligands and to influence control over the regio- and stereoselectivity of the reaction.[11] The stable complexes help to prevent reaction pathways leading to the undesired coupling product.

4.14.2.4 Bases

There are multiple roles for the bases in the Heck reaction such as: regeneration of Pd(0) from the Pd(II)-hydride intermediate, preactivation and reduction of Pd(II) precatalysts, cleavage of slow-release catalysts to the catalytically active species, and functioning as a labile ligand to stabilize Pd(0). Pd(II)-hydride intermediates are quite acidic and as such strong bases are not required for their deprotonation to reform Pd(0). It is known that the Heck reaction does take place in the absence of base, however, it is quenched after a limited number of turnovers. From this, it can be deduced that the function of the base is important to prevent the build-up of acidity in the reaction media to achieve turnover of the catalyst rather than solely for the deprotonation of the Pd(II)-hydride intermediate. Support of this argument is the base-free Heck reaction with aryl diazonium salts which requires high catalyst loadings.[16] The most common bases for the Heck reaction are tertiary amines (e.g., Et_3N/Bu_3N) in nonpolar solvents for ligand-assisted protocols, inorganic bases (e.g., acetates/carbonates/phosphates) in polar coordinating solvents for simple Pd salts and slow-release catalysts, nonnucleophilic bases (Hünig's base, Cy_2NEt, proton sponge) for use in type 3 and type 4 processes (well-defined Pd sphere). Strong Lewis bases (tetramethylguanidine, 1,4-diazabicyclo[2.2.2]octane (DABCO)) have also been used in phosphine-free systems and shown to improve yields, possibly acting as ligands.[17]

4.14.2.5 Additives

The most significant use of additives is the Jeffrey–Larock protocol where the Heck reaction is carried out using Pd(II) salts in aqueous solvents with a quaternary ammonium salt additive such as tetra-*n*-butylammonium bromide (Bu_4NBr).[18] A number of other salt additives are common and are generally applied to reactions of aryl iodides under mild conditions in type 1 systems or to less reactive substrates under harsh conditions in type 2 systems (Section 4.14.2.4). The possible functions of these additives are to exchange an iodide ligand for a more labile chloride/bromide/acetate ligand, to form an anionic Pd complex, to aid the preactivation step and/or to help stabilize small clusters of Pd(0) in solution. Other common additives are Ag(I) and Tl(I) salts which act as halide scavengers to leave a vacant coordination site for an alkene, thus enabling reactions via the cationic pathway without the need for employing an aryl triflate/diazonium salt.

4.14.2.6 Reaction Media

There has been extensive research in the reaction media used for the Heck reaction (Section 4.14.10). Depending on the catalytic system employed there is a preference for nonpolar and low Lewis basicity or polar and high Lewis basicity. Type 1 and type 2 systems prefer polar media to aid deligation of the halide and to help support the Pd catalyst, such as DMF, dimethylacetamide (DMA), *N*-methylpyrrolidone (NMP), and dimethylsulfoxide (DMSO) or aqueous solvents or ionic liquids (ILs). Type 3 systems prefer nonpolar solvents such as toluene, 1,4-dioxane, or THF. Numerous other systems have been reported such as supercritical CO_2, fluorous systems, aqueous systems, and solvent-free systems.[19]

4.14.2.7 Reaction Temperature

The temperature at which the Heck reaction is carried out depends on the type of catalyst used. More recently designed precatalysts have a high thermal stability and therefore require high reaction temperatures to generate the catalytically active species. In type 2 systems (Section 4.14.2.1) high temperatures may be needed to speed up the oxidative addition step. In type 3 and type 4 systems, where Pd has a well-defined coordination sphere, higher temperatures may have an adverse effect on reactivity and selectivity. Room temperature Heck reactions can be achieved when aryl iodides are coupled with activated alkenes over long reaction times and there is even an example of Pd nanoparticles promoting reactions at low temperatures.[20]

4.14.2.8 Development of Catalysts for Unactivated and Deactivated Aryl Chlorides

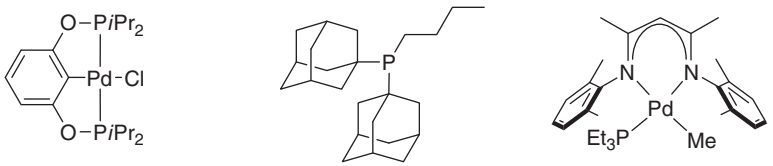
As early as 1973, the Heck-coupling of chlorobenzene with styrene was achieved by Julia using Pd on charcoal as the catalyst giving a 62% yield of stilbene.[21] Davidson made the first significant progress in the homogeneous Heck reaction of unactivated aryl chlorides in 1984. Chlorobenzene was successfully reacted with styrene in a modest yield of 53% using the bidentate phosphine ligand 1,2-bis(diphenylphosphino)ethane (dppe).[22] Milstein successfully carried out the vinylation of chlorobenzene using the bulky, electron-rich and chelating bidentate phosphine 1,4-bis(diisopropylphosphino)butane (dippb) at elevated temperatures of 150 °C.[23] Since the ligand was bidentate, catalysis most likely proceeded via the cationic pathway, limiting the effectiveness of the system. In 1998, Reetz reported the coupling of chlorobenzene with styrene using simple Pd salts such as $PdCl_2$ or $Pd(OAc)_2$ in the presence of tetraphenylphosphonium salts.[24]

Independently, Fu and Hartwig developed the most broadly applicable catalyst system for the coupling of unactivated aryl chlorides using $P(Bu^t)_3$ as the bulky, electron-rich ligand. Fu reported the use of $Pd_2(dba)_3$ with $P(Bu^t)_3$, Cs_2CO_3 in 1,4-dioxane at 100–120 °C to couple electron-rich and hindered aryl chlorides with styrene/methyl acrylate.[14b] They subsequently improved the reactivity of the system by replacing Cs_2CO_3 with the sterically hindered amine Cy_2NMe, thus extending the scope of the olefin-coupling partner to mono and disubstituted olefins with both electron-rich and hindered aryl chlorides.[25] Under these conditions 4-chloroanisole could be successfully coupled with styrene in a yield of 72%. Fu also demonstrated that the air-sensitive $P(Bu^t)_3$ could be directly replaced by air stable tri(*t*-butyl)phosphonium salts.[26] Hartwig used a fluorescence-based assay to screen over 40 phosphine ligands and found that only $P(Bu^t)_3$ and di(*t*-butyl)phosphinoferrocene (dppf) were useful for the coupling of unactivated aryl chlorides. The optimal catalytic system described used $Pd(dba)_2$, $P(Bu^t)_3$, with NaOAc in DMF at 110 °C.[14a]

The polymer-bound heterogeneous catalyst dichloropalladium(di(pyrid-2-yl)amide) allowed the reaction of chlorobenzene and styrene to be carried out with high TONs (24 000) when Bu_4NBr was added to form stilbene in 89% yield.[27] Hermann reported the use of nonaqueous ILs as an excellent media for carrying out Heck reactions of unactivated aryl chlorides using a phospha-palladacycle catalyst.[28] Jensen carried out the coupling of styrene with unactivated chlorobenzene and deactivated 4-chloroanisole in yields of $>99\%$ and 88%, respectively, using a phosphinito phosphorus-carbon-phosphorus (PCP) pincer complex **15** (Figure 2).[29] These complexes are postulated to proceed through a Pd(II)/Pd(IV) catalytic cycle. Beller described the use of a 1-adamantyl-*n*-butylphosphine ligand **16** (Figure 2) with an increased yield of 98% (vs. 94%) for the Heck-coupling of 4-chlorotoluene with styrene and a yield of 82% for the reaction of deactivated 4-chloroanisole with 2-ethylhexyl acrylate.[30] A number of bulky, electron-rich phosphines were screened and only 1-adamantyl-*n*-butylphosphine and $P(Bu^t)_3$ afforded good yields.

Jin described the synthesis of a β-diketiminatophosphine complex **17** (Figure 2) for the Heck-coupling of a wide range of chloroarenes including some electron-rich and sterically hindered examples.[31] The reactions were carried out under relatively mild

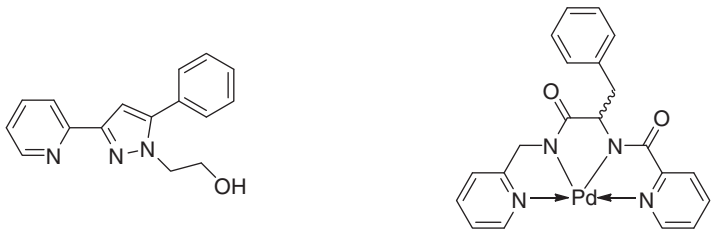
conditions in aqueous DMF at 85 °C. The widely accepted benchmark substrate for deactivated aryl chlorides, 4-chloroanisole, however, was not tested using this catalyst.



15 16 17

Figure 2 Catalysts/ligands for aryl chloride substrates.

Pons and Branchadell reported the use of a nonphosphine containing ligand for the coupling of chlorobenzene with *t*-butyl acrylate using pyridylpyrazole ligands, e.g., **18** (Figure 3). They achieved a yield of 97% over an extended reaction time of 51 h using a very low catalyst loading (0.01 mol%) for the Heck coupling of unactivated aryl chlorides.[32] Another phosphine-free system was described by Kantam where a N4-tetradentate dicarboxyamidate/dipyridyl Pd complex **19** (Figure 3) was employed to couple 4-chloroanisole with styrene in a 62% yield.[33] It is important to note that majority of the above systems described for unactivated aryl chlorides can promote the Heck coupling of a wide range of aryl bromides under very mild conditions.

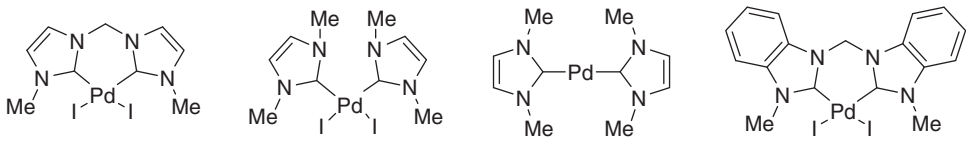


18 19

Figure 3 Phosphine-free ligand/catalyst for aryl chloride coupling partners.

4.14.2.9 Carbene Complexes

Recent developments in ligand design have shown that heterocyclic carbene ligands are the most important class of nonphosphine-containing ligands at effectively imitating the bulky electron-rich phosphine ligands.[34] Seminal work in this area was carried out by Hermann, who applied Pd complexes of dimethyl *N*-heterocyclic carbenes (NHCs) **20–22** (Figure 4) to the Heck reaction of aryl chlorides and bromides.[35] The complexes were used either as preformed complexes or as mixtures of Pd and imidazolium salts and were used to effectively carry out the Heck coupling of activated and deactivated aryl bromides as well as activated aryl chlorides. The reactions were carried out at 125–140 °C in DMA with aryl chlorides requiring the addition of Bu_4NBr. Faster reaction times were afforded using the preformed Pd(0) complex with an 800-fold increase in activity. Both the chelating and nonchelating analogs showed long induction periods, indicating a slow conversion into the active species. The use of carbene ligands in the Heck reaction normally requires polar aprotic solvents such as DMF, DMA, or NMP at 120–170 °C with sodium acetate commonly used as a base and Bu_4NBr as a common additive.

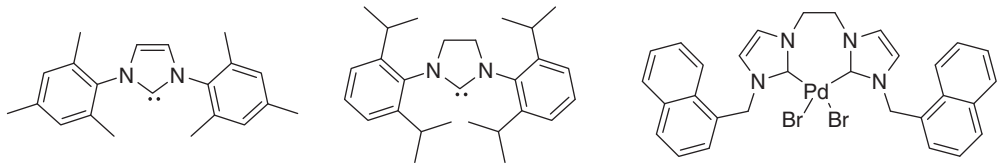


20 21 22 23

Figure 4 NHC catalysts in the Heck reaction.

Biffis found that increasing the steric bulk of complex **20** by changing the *N*-Me to Ph or by using a benzimidazolyl-2-ylidine **23** (Figure 4) led to a significant increase in TON.[36] These dicarbene complexes performed as well as $Pd(OAc)_2$ alone when

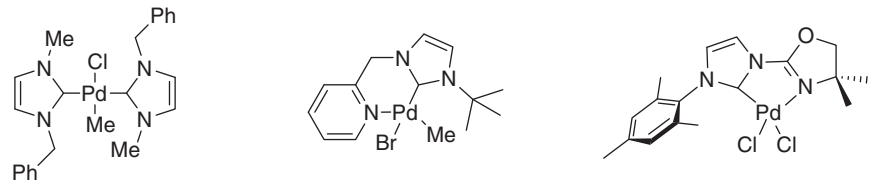
activated aryl bromides were employed, however, they were not as active as $Pd(OAc)_2$ when deactivated aryl bromides were used. Detailed kinetic analysis revealed that the catalytically active species involved a coordinated dicarbene ligand. The use of sterically hindered carbenes IMes and SIPr (Figure 5), originally developed for olefin-metathesis, were shown to be useful ligands for the Heck coupling of a range of aryl bromides in high yields.[37] Lee reported the coupling of 4-chlorotoluene with styrene in 72% yield using 3 mol% of an *N*-naphthyl-substituted bis-carbene Pd complex **26** (Figure 5).



24 IMes **25** SIPr **26**

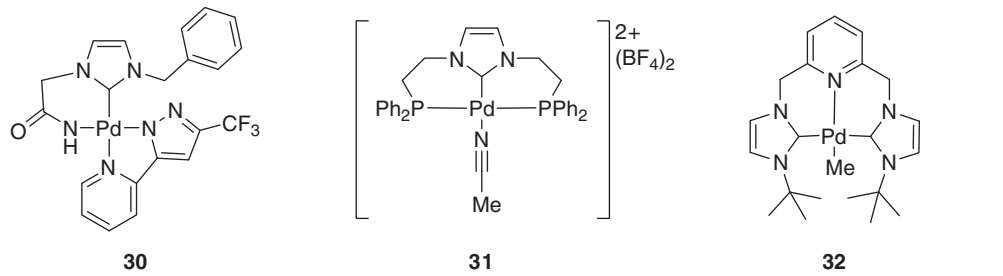
Figure 5 Sterically hindered NHC catalysts.

Incorporation of a methyl group on Pd by Cavell drastically increased the catalytic activity of the complex **27** (Figure 6) for the coupling of 4-bromoacetophenone with *n*-butyl acrylate as demonstrated by the high TON (980 000).[38] A complex containing an NHC linked via a methylene bridge to a pyridine donor **28** (Figure 6) has shown very high TONs (2 858 000) for the coupling of iodobenzene with methyl acrylate. Gade applied a monocarbene complex **29** (Figure 6) with an oxazoline as the *N*-donor.[39] Successful coupling of 4-chloroacetophenone and styrene was achieved in 92% yield using 0.2 mol% catalyst. A Pd complex with a bidentate carbene/amido donor ligand used in conjunction with a bidentate pyridyl-pyrazolate ligand was reported by Lee to be an effective catalyst for the coupling of 4-chloroanisole with styrene in 82% yield using 0.5 mol% catalyst **30** (Figure 7).[40]

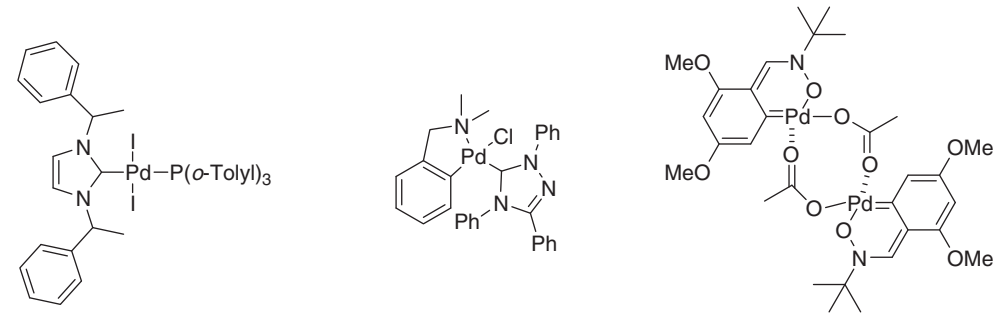


27 **28** **29**

Figure 6 Pd-NHC-complexes with increased catalytic activity.



30 **31** **32**



33 **34** **35**

Figure 7 Pincer, hybrid and palladacyclic-NHC-catalysts.

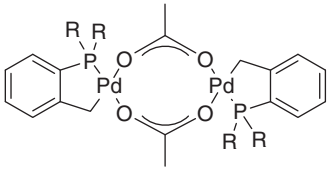
Another subclass of carbene complexes are those contained in a tridentate pincer system of CNC, NCN, PCP, and CCC type-complexes. A PCP–carbene–pincer complex reported by Lee displayed record high TONs of 56 000 000 in the coupling of iodobenzene with styrene using a dicationic complex **31** (Figure 7).[41] Cavell reported the use of a number of CNC–pincer ligands with high activity in Heck coupling reactions. The reaction of 4-bromoacetophenone with *n*-butylacrylate using 0.001 mol% of complex **32** (Figure 7) proceeded with 73% conversion with a TON of 72 700.[42] A number of hybrid carbene–phosphine ligands have also been tested but their Pd complexes did not show any dependence on the phosphine ligand, possibly since deligation of the phosphine is likely to occur first at the reaction temperature employed. Herrmann reported the use of a number of NHC–Pd–phosphine complexes with **33** showing the highest activity in the coupling of 4-bromoanisole with styrene in 98% yield using 1 mol% catalyst.[43] NHC-ligated complexes have also been shown to be suitable catalysts for the Heck reaction. For example, the phosphine palladacycle **34** (Figure 7) successfully coupled 4-bromoanisole and 4-chloroacetophenone with styrene in 81% and 97% yields, respectively.[44] A number of carbocyclic carbene ligands have been synthesized and applied to the Heck reaction. One of the most prevalent examples is the ligand derived from an aromatic nitrone. Catalyst **35** (Figure 7) allowed 4-bromoanisole and styrene to be coupled with a very low catalyst loading of 8×10^{-5} mol% giving a yield of 75% and a TON of 937 500, albeit over an extended reaction time of 169 h at 140 °C.[45]

The high temperatures under which Pd–carbene complexes are used in the Heck reaction make it difficult to understand the active catalyst involved. It is generally accepted that the stabilizing effect of carbene ligands allow these complexes to act as slow-release precatalysts, providing a reservoir of catalytically active Pd, without the formation of Pd black.

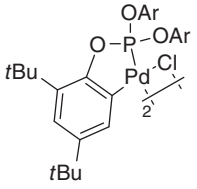
4.14.2.10 Palladacycles

These are possibly the most widely studied class of ligands for the Heck reaction. The majority of palladacycles are able to promote the coupling of a range of aryl iodides and bromides at high temperatures in the presence of a base and often with an additive such as Bu_4NBr. Palladacycles most likely act as a reservoir of the catalytically active Pd(0) species, owing to the high stability of these complexes even at elevated temperatures up to 140 °C. The temperature at which the catalyst releases the active Pd(0) species depends on the nature of the palladacycle, be it five- or six-membered, phosphorus or phosphorus-free or even pincer type. When introduced in the Heck reaction, palladacycles allowed very small concentrations of catalyst (0.001 mol%) to be used for the coupling of activated aryl bromides whereas prior to their introduction 0.5–5 mol% was required. Computational DFT studies indicate that palladacycles appear to be activated by insertion of the alkene into the Pd–C bond and subsequent *β*-hydride elimination.[46]

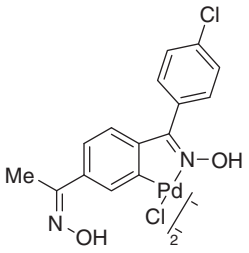
The introduction of the Hermann–Beller palladacycle provided the first commercially available and effective catalyst which allowed coupling of 4-bromoanisole with *n*-butyl acrylate in 87% yield using 0.5 mol% palladacycle **36** (Figure 8).[47] This seminal study showed that the activated aryl chlorides could also undergo Heck-coupling with the addition of Bu_4NBr. The palladacycle was found to only react with aryl bromides in the presence of an olefin-coupling partner. This palladacycle is capable of catalyzing the Heck reactions of aryl bromides achieving high TONs (200 000 in DMA, 1 000 000 in nonaqueous IL Bu_4NBr). Bedford reported a highly active triarylphosphite palladacycle **37** (Figure 8) giving very high TONs for the coupling of 4-bromoacetophenone and styrene of up to 5 750 000 and showed excellent activity for coupling of deactivated 4-bromoanisole with *n*-butyl acrylate (TON = 9800, 98% conversion).[48] An oxime-derived, phosphorus-free palladacycle **38** (Figure 8) developed by Nájera was shown to be a very efficient Heck coupling catalyst. This catalyst showed high activity in the Heck coupling of aryl iodides and deactivated aryl bromides (TON up to 97 000) and activated aryl chlorides.[49]



36 (R = 2-tolyl)



37 (Ar = 2,4-$Bu^t_2C_6H_3$)

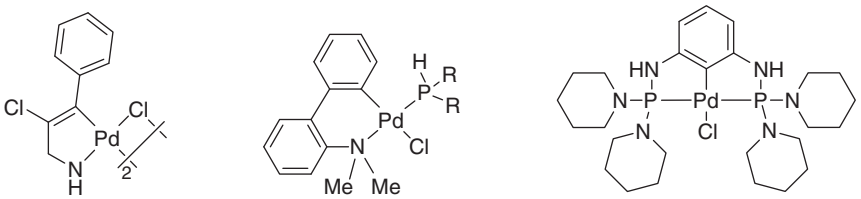


38

Figure 8 Palladacycle catalysts in the Heck reaction.

Another highly active phosphorus-free palladacycle was described by Dupont and showed the first room temperature example of a Heck coupling with a palladacycle.[50] The chloropalladated propargylamine **39** (Figure 9) is less stable and has the ability to release catalytically active Pd(0) at lower temperatures. The coupling of iodobenzene with *n*-butyl acrylate at 30 °C gave quantitative yields of the coupled product albeit with 1 mol% catalyst. At elevated temperatures (150 °C) 4-bromoanisole could also be coupled with *n*-butyl acrylate in 72% yield with 0.01 mol% catalyst. Indolese described the combination of a CN-palladacycle with a secondary phosphine **40** (Figure 9) and reported the coupling of 4-chloroanisole with *n*-butyl acrylate in quantitative

conversions with 1 mol% catalyst at 140 °C.[51] An aminophosphine-based pincer palladabicycle **41** (Figure 9) was shown to promote the Heck coupling of a range of deactivated and sterically hindered aryl bromides with low catalyst loadings and short reaction times.[52] The high activity was demonstrated with a large-scale coupling of bromobenzene with styrene using 0.00002 mol% of the palladabicycle, achieving quantitative yield in 36 h. This catalyst was also able to process deactivated and sterically hindered aryl chlorides albeit at higher reaction temperatures. A large number of other palladacycles have been synthesized to date and are useful catalysts for more reactive substrates such as aryl iodides and activated aryl bromides, including PCP–, NCN–, and SCS–pincer palladabicycles.[11,53]

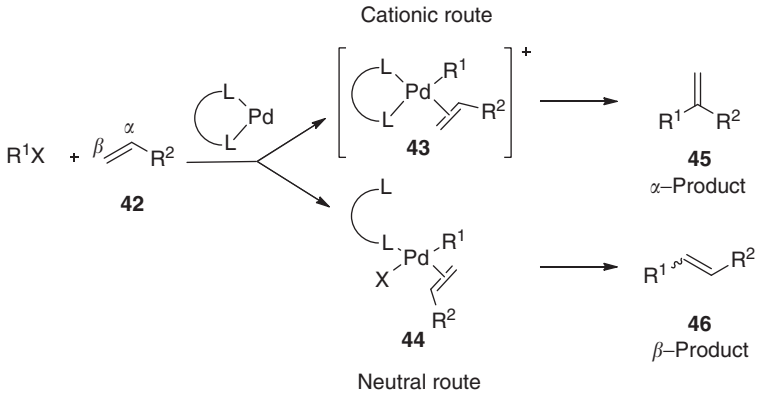


39 **40** **41**

Figure 9 Further development of palladacycle catalysts for the Heck reaction.

4.14.3 Regioselectivity

There are three possible products following a Heck reaction, depending on which position of the alkene (α or β) the aryl group adds to (Scheme 2). The product outcome is dependent on which of the two catalytic cycles the reaction proceeds through (see Section 4.14.2.1).



Scheme 2

4.14.3.1 Influence of ArX on Catalytic Cycle

If the reaction proceeds through the cationic catalytic pathway the bidentate ligand remains bound to Pd with loss of X following coordination to the alkene. If X is a good leaving group such as a triflate then this pathway is favored. However, aryl triflates are labile and often not commercially available. If X is a halide it is not as easily lost, favoring the neutral pathway. One option is to use halide scavengers such as silver or thallium salts in stoichiometric quantities, although this adds to the cost and toxicity.[54] Recent developments have enabled the use of aryl halides, including chlorides, in the synthesis of the branched products. Substituents on the aryl group also influence the reactivity; electron-donating groups accelerate the reaction, whereas electron-withdrawing groups diminish reactivity.

4.14.3.2 Influence of Olefin on the Product Outcome

Electron-poor olefins give rise to linear products, whereas electron-rich olefins favor the cationic pathway and give rise to branched products (Figure 10).[55]

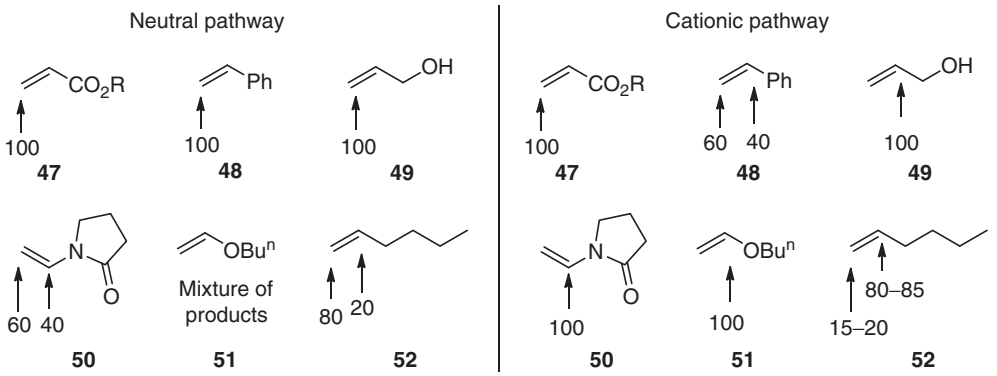
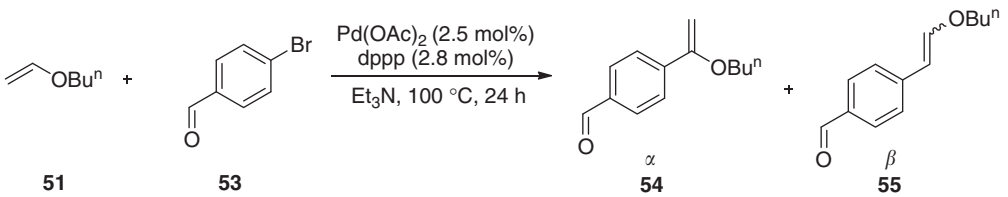


Figure 10 Regioselective outcome associated with reaction pathway.

4.14.3.3 Influence of Solvents on the Regioselectivity of the Heck Reaction

Xiao developed the use of ILs in the regioselective Heck arylation of electron-rich olefins.[56] They showed that the cationic pathway was favored when the solvent employed was an IL, as it promotes the formation of the charged Pd species following coordination with the olefin. This charged species is then stabilized by the electrostatic interactions with the IL. The IL employed in these investigations was 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]). The reaction between butyl vinyl ether (**51**) and 4-bromobenzaldehyde (**53**) with $Pd(OAc)_2$ as the precatalyst, dppp as the bidentate ligand and Et_3N as the base was performed in a series of different solvents (**Table 1**). The IL gave 100% conversion with excellent α-regioselectivity. Toluene and CH_3CN gave poor conversions and a mixture of products. The polar solvents DMF and DMSO gave high conversions but a mixture of the regioisomers. Previous work by Hallberg demonstrated that a mixture of DMF–H_2O as the solvent gave high regioselectivity in the reaction between aryl bromides and vinyl ethers.[9]

Table 1 Regioselectivity associated with different solvents

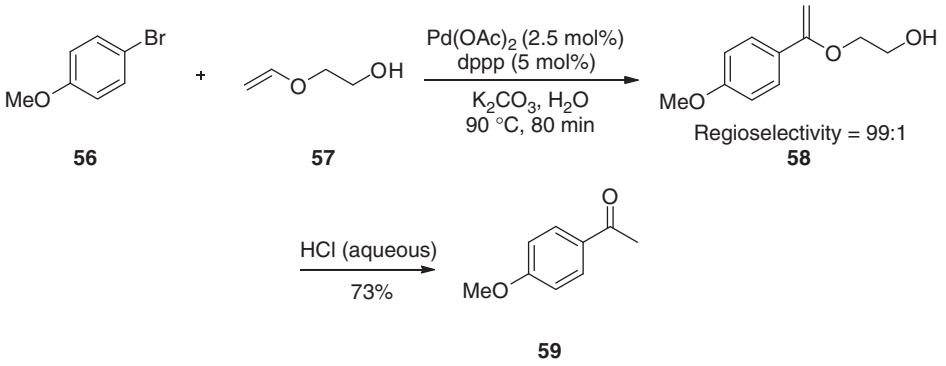


Solvent	*Conversion (%)*	*α/β*
[bmin][BF_4]	100	>99/1
toluene	18	47/53
CH_3CN	33	45/55
DMF	100	47/53
DMSO	100	86/14

Larhed later demonstrated that the Heck reaction with electron-rich olefins can be performed with excellent regioselectivity in H_2O.[57] The reaction was performed with $Pd(OAc)_2$, dppp, and K_2CO_3. The reaction between 4-bromoanisole and ethylene glycol vinyl ether gave the α-product which was then hydrolyzed in acid to generate the ketone in good yield (**Scheme 3**). The regioselective Heck reaction was performed between vinyl ethers and aryl iodides/aryl chlorides under these conditions. Using $Pd(dippp)_2$ (dippp = 1,3 diisopropylphosphino)propane) as the catalyst allowed the regioselective reaction between selected aryl chlorides and electron-rich olefins to be performed.

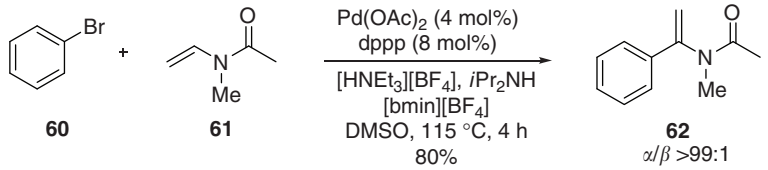
4.14.3.4 Hydrogen Bond Donors in the Regioselective Heck Reaction

Xiao showed that hydrogen bond-donating ammonium salts could be used to form the α-product with high regioselectivity in both ILs and common solvents such as DMF.[58] The reaction times were increased on performing the reaction in DMF in place of ILs. By adding hydrogen bond donor salts such as [$HNEt_3$][BF_4] or [H_2NiPr_2][BF_4] the reaction rate was greatly increased, although this augmentation was not seen in the presence of [NBu_4][BF_4]. The reactions between aryl bromides and enamides/vinyl ethers gave excellent selectivity in DMSO with the hydrogen bond donor (equation 2).



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

Scheme 3

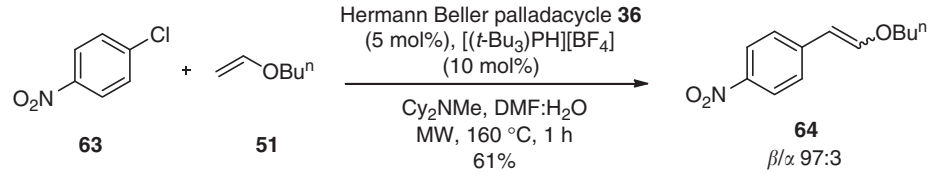


60 **61** **62**
α/β >99:1

(2)

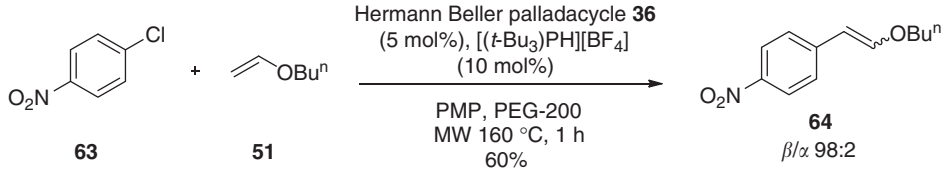
4.14.3.5 Selective β-Arylation

Larhed demonstrated that aryl chlorides can react with vinyl ethers under certain conditions to give the linear product.[59] The reaction was subjected to MW irradiation with Fu's $P(Bu^t)_3$ ligand.[60] The source of the ligand in the MW reaction was $[(Bu^t)_3PH][BF_4]$. Both PEG-200 and DMF were suitable solvents. The bases used were either 1,2,2,6,6-pentamethylpiperidine (PMP) or Cy_2NMe. The regioselectivities for the different solvent/base combinations examined were comparable in all reported examples (equations 3 and 4).



63 **51** **64**
β/α 97:3

(3)



63 **51** **64**
β/α 98:2

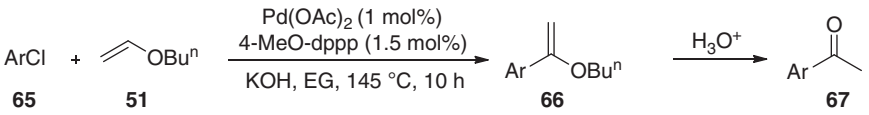
(4)

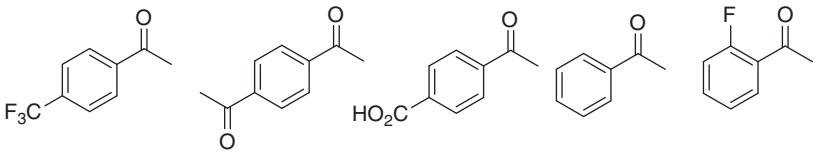
4.14.3.6 General Conditions for α-Selective Heck Reaction with Aryl Chlorides

Although there were previous examples of the regioselective Heck reaction between aryl chlorides and electron-rich alkenes the methodologies were not suitable for a broad range of substrates, *vide supra*. Recently, significant progress has been made in this area, expanding the scope of the regioselective Heck reaction to include a vast array of aryl chlorides.[61] Optimization of the reaction involving aryl chlorides led to the use of the modified dppp ligand, 4-MeO-dppp. At catalyst loadings of 1 mol%, this more electron-rich ligand gave much higher conversions (88%) than the dppp ligand (40%), whereas the electron-deficient 4-CF_3-dppp ligand gave a yield of $<2\%$. The reaction conditions tolerated both activated and unactivated aryl chlorides as well as *ortho*-, *meta*- and *para*-substituted aryl chlorides (Table 2). The use of ethylene glycol (EG) as the solvent for the reaction was imperative for its success.

These studies also involved variation of the alkenes. High levels of regioselectivity were maintained for other electron-rich olefins such as enamides and also unactivated olefins.

Table 2 Regioselective Heck reaction with aryl chlorides in the synthesis of ketones





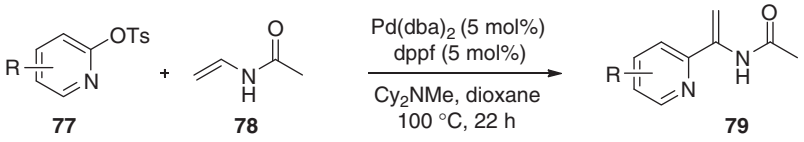
68 (70%) **69** (90%) **70** (72%) **71** (83%) **72** (72%)

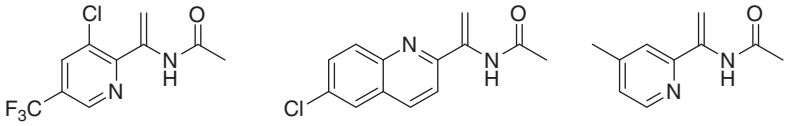
73 (72%) **74** (88%) **75** (76%) **76** (90%)

4.14.3.7 Heteroaromatic Tosylates in the Regioselective Heck Reaction

Recently, Skrydstrup performed a Heck reaction with heteroaromatic tosylates and electron-rich alkenes to give the branched α-product in high yields.[62] The use of aryl tosylates is beneficial as they are cheaper and more stable than their corresponding triflates. The use of dppf as the ligand with Pd(dba)$_2$ as the Pd source, together with Cy$_2$NMe as the base, led to the desired product (Table 3). This reaction proceeded in the presence of aryl chlorides but was chemoselective for the tosylate, leaving a functional handle for further manipulation of the product.

Table 3 Regioselective Heck reaction with *N*-vinyl acetamide

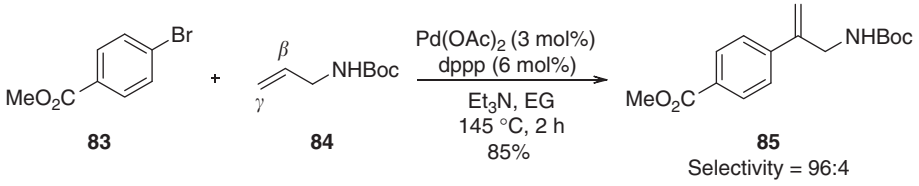




80 (68%) **81** (72%) **82** (74%)

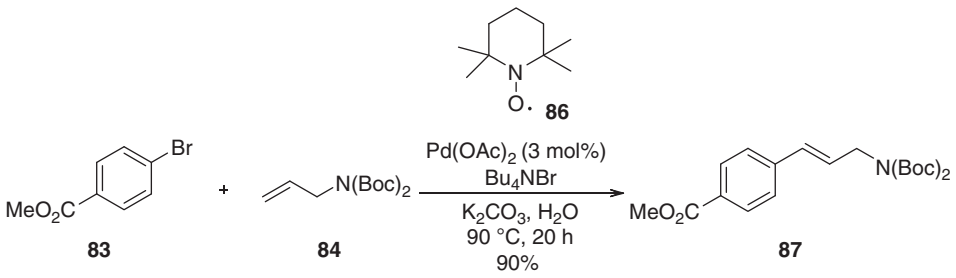
4.14.3.8 Control of Regioselectivity with Allylamines

A recent report by Xu demonstrated that the β/γ regioselectivity associated with the Heck reaction of allylamines can be controlled by carefully choosing the reaction conditions.[63] The use of EG as the solvent and dppp as the bidentate ligand favored the cationic pathway and β-selectivity (equation 5).



(5)

Changing the solvent to H_2O, with the addition of the free radical scavenger, TEMPO, to accelerate the reaction, and addition of the quaternary ammonium salt, Bu_4NBr, gave excellent γ-selectivity (equation 6). The neutral pathway was promoted as the reaction was ligand-free. The use of quaternary ammonium salts under ligand-free conditions, known as Jeffrey conditions, is known to generate the linear product.[64] The careful manipulation of reaction conditions and slight modification of the substrate led to reversal of selectivity in this case.

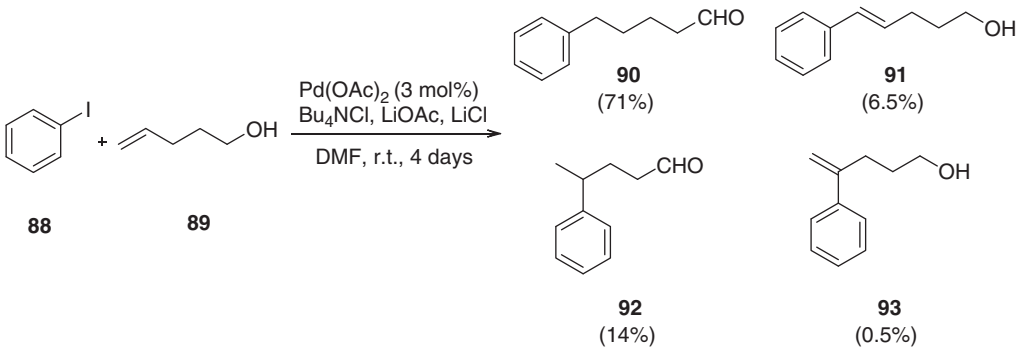


(6)

4.14.3.9 Migration of Double Bond

There are issues associated with performing the Heck reaction, particularly the asymmetric Heck reaction on dihydrofurans, as migration of the double bond can occur (Section 4.14.8.1).

Larock found that the reaction between iodobenzene and a nonallylic unsaturated alcohol gave rise to a mixture of products (equation 7).[65] The aryl group added to both terminal and internal carbons of the olefin. Migration of the double bond along the chain also occurred resulting in the formation of the aldehyde.



(7)

4.14.4 Cyclization

4.14.4.1 Introduction

This section will cover the formation of cyclic structures using the Heck reaction. The selected examples of cyclization discussed herein are categorized according to the Baldwin rules,[66] which provide a system to predict the favorability of cyclization (**Table 4**). These rules/guidelines categorize the reaction by the size of the ring formed, the method of cyclization (with *exo* for the double bond external to the cycle or *endo* for an internal alkene) and the geometry of the carbon undergoing cyclization (e.g., 5-*exo*-*trig*). Only *trig* cyclizations will be covered in this section as these are classified as reactions that proceed with addition of the carbopalladium complex to a double bond.

Table 4 Baldwin rules for *trig* reactions

3		*4*		*5*		*6*		*7*	
Exo	*Endo*	*Exo*	*Endo*	*Exo*	*Endo*	*Exo*	*Endo*	*Exo*	*Endo*
F	DisF	F	DisF	F	DisF	F	F	F	F

Abbreviations: DisF = Disfavored; F = Favored.

The Heck reaction is often employed in cyclization steps, as this versatile reaction generally uses simple precursors that are readily available or easily prepared. Also a wide range of ring sizes can be formed using this Pd-catalyzed intramolecular methodology; three- to nine-membered rings can be formed using an *exo-trig* cyclization with six- to nine-membered rings being formed by *endo-trig* cyclization preferentially.

Five- to seven-membered rings are the most common and these cyclizations will be discussed in detail whereas smaller rings, larger rings, and macrocyclizations will only be discussed briefly.

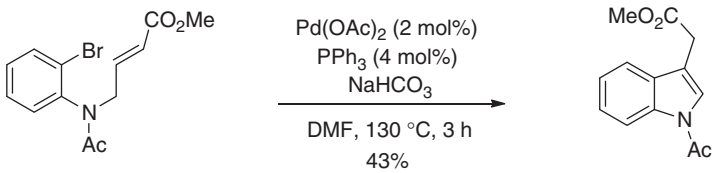
The use of the Heck reaction for cyclizations was first reported in the late 1970s. Initially this methodology was applied for the synthesis of heterocycles.[67] The first publications on carbocyclization using the Heck reaction were in the late 1980s. Grigg,[68] Negishi,[69] and Heck[70] all contributed to the field at this time. The early publications reported low yields and so their application to the synthesis of complex natural products was limited. Momentum in this field increased over the next few years with developments from Grigg,[71] Overman,[72] Larock,[73] and Negishi[74] and more recently Fuchs[75] in the early 1990s.

As can be seen now from the extensive body of literature, the most dominant mode of cyclization is the *exo*-mode with five- to seven-membered rings being most commonly formed. *Endo* cyclization is mostly seen in the synthesis of six- and seven-membered rings as well as larger rings. Negishi has referred to this mode of cyclization as an 'apparent' *endo* cyclization mode as he postulated that these reactions are most likely incorrectly assigned and are more likely to proceed through an augmented version of a more favored reaction pathway. It is proposed by Negishi to be an unusual *exo*-mode cyclization followed by cyclopropanation, rearrangement, and β-dehydropalladation.[76] We will consider the reactions as originally assigned, *endo-trig* cyclizations.

4.14.4.2 Medium/Common Ring

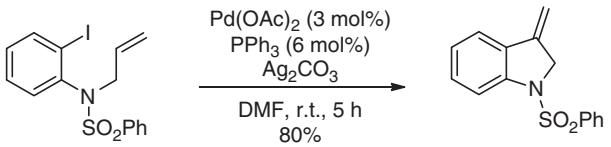
4.14.4.2.1 5-Exo-trig

The first intramolecular Heck cyclization was reported by Mori for the synthesis of indole and indole-containing compounds.[67] After testing a variety of halogenated starting materials it was found that the brominated starting material gave the highest yield of the aromatic product (**95**) at 43% (equation 8).



94 **95** (8)

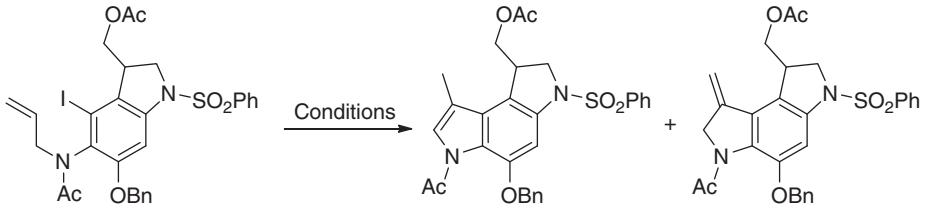
The product formed is the 5-*exo-trig* product but double-bond isomerization gives the more stable, *endo*-cyclic product by a second *syn*-elimination after reinsertion of the Pd into the double bond. This can be prevented in most cases by the addition of Ag_2CO_3, giving the nonaromatic product (**97**) (equation 9).[77]



96 **97** (9)

Another way to stabilize the product to double-bond isomerization is to employ the Jeffery conditions, as shown by Tietze. In this methodology there is selective formation of the *endo*- or *exo*-cyclized product depending on reaction conditions employed (**Table 5**).[78]

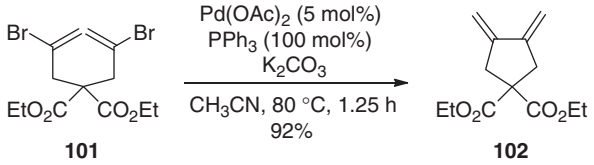
Table 5 Selective formation of the *endo*- or *exo*-cyclized product



98 **99** **100**

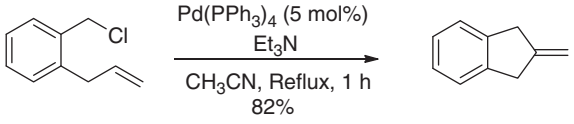
Entry	*Conditions*	***99*** *(%)*	***100*** *(%)*
i	$Pd(OAc)_2$ (20 mol%), NaOAc, Bu_4NCl, DMF	30	64
ii	$Pd(PPh_3)_4$ (5 mol%), Et_3N, CH_3CN	70	10

The original carbocyclization using the Heck reaction was published by Grigg.[79] Acyclic 2-bromo-1,6-heptadienes were studied giving 1,2-dimethylenecyclopentanes with low regioselectivity and with a competitive 6-*endo-trig* mode of cyclization. Further work by Grigg[80] allowed exclusive formation of the 5-*exo-trig* product in 92% yield using a β-elimination of bromine, which prevented double-bond migration (equation 10).



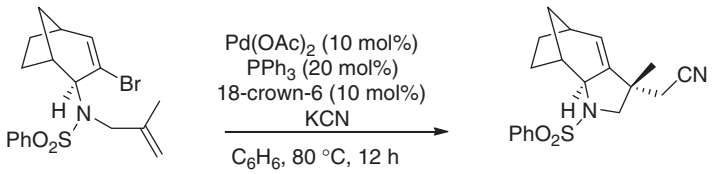
101 **102** (10)

Negishi[81] further developed the intramolecular 5-*exo-trig* cyclization, applying the methodology to benzyl chlorides to afford high yields with no double-bond migration (equation 11).



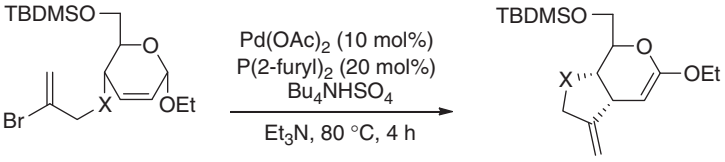
103 **104** (11)

Supplementary to his work on carbocyclizations, Grigg also contributed to the heterocyclization methodology development.[82] In addition, he developed methodology for the capture of anions during cyclization by a wide range of anionic, neutral, and organometallic reagents (equation 12).[83] Regio- and stereoselectivity can be induced using this method of trapping.[84]



105 **106** (12)

In an attempt to synthesize the template of carbohydrates using the Heck reaction, Sinou developed a cyclization procedure using alkyl substrates.[85] This procedure is used to generate bi- or tricyclic systems in high yields using mild reaction conditions. This heterocycle can either be nitrogen- or oxygen-containing, both of which give high yields (equation 13).



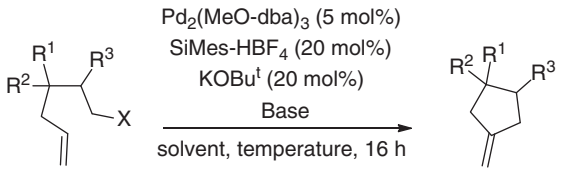
107a X = NTs
107b X = O

108a X = NTS (81%)
108b X = O (77%) (13)

Fu has also applied the carbocyclization methodology to so-called alkyl-Heck reactions.[86] Using an unactivated electrophile as the substrate it was possible to synthesize a wide range of products (**Table 6**). These were performed on a novel class of alkyl bromide and chloride Heck substrates with the highest yields obtained with the alkyl bromides. Although these substrates contain a β-hydrogen that could lead to the formation of byproducts, the conditions used in the reaction prevented the formation of this side-reaction.

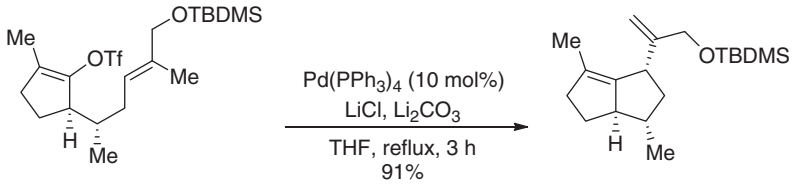
Grigg has performed Heck reactions on strained substrates including vinyl halides, substrates that were not often previously applied in this methodology.[71b] Paquette has applied more strained reagents such as vinyl triflates and aryl triflates in the formation of fused carbocycles (equation 14).[87] Negishi[74b] has also varied the substitution on the alkene portion of the substrate, using cyclic alkenes.

Table 6 Alkyl-Heck reactions of unactivated alkyl halides



109 **110**

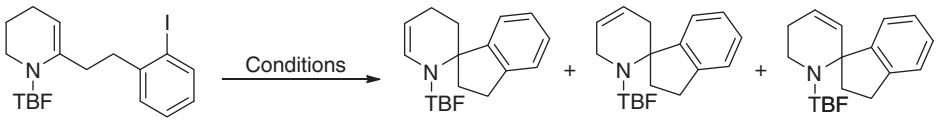
Substitution	*Solvent*	*Temperature (°C)*	*Base*	*X*	*Yield (%)*
$R^1=R^2=CO_2Et$, $R^3=H$	CH_3CN	65	Cs_2CO_3	Br	85
$R^1=R^2=CO_2Et$, $R^3=H$	NMP	100	K_3PO_4	Cl	80
$R^1=H$, $R^2=n$OCt, $R^3=H$	CH_3CN	65	Cs_2CO_3	Br	75
$R^1=H$, $R^2=n$OCt, $R^3=H$	NMP	100	K_3PO_4	Cl	71
$R^1=H$, $R^2=H$, $R^3=n$OCt	CH_3CN	65	Cs_2CO_3	Br	73
$R^1=H$, $R^2=H$, $R^3=n$OCt	NMP	100	K_3PO_4	Cl	66



111 **112** (14)

Further studies were subsequently undertaken by Hallberg to apply this methodology to the preparation of alkenes in heterocycles, specifically cyclic enamines (Table 7).[88] This work was undertaken in an effort to reduce the double-bond migration that occurs post-Heck reaction. This aim was achieved, with selective formation of all regioisomers formed by using carefully selected catalytic systems. This methodology was further applied to the synthesis of the 6-*exo-trig* product using a longer chain length between the enamine and aryl group.

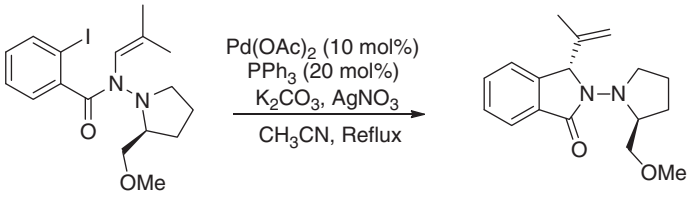
Table 7 Heck reaction on cyclic enamines



113 **114** **115** **116**

Products	*Conditions*	*Yield (%)*
114	$Pd(OAc)_2$ (5 mol%), K_2CO_3, CH_3CN, 100 °C, 96 h	54
115	$Pd(OAc)_2$ (10 mol%), BINAP (20 mol%), Et_3N, cyclohexene, CH_3CN, 80 °C, 20 h	54
116	$Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), TlOAc, Et_3N, CH_3CN, 80 °C, 17 h	79

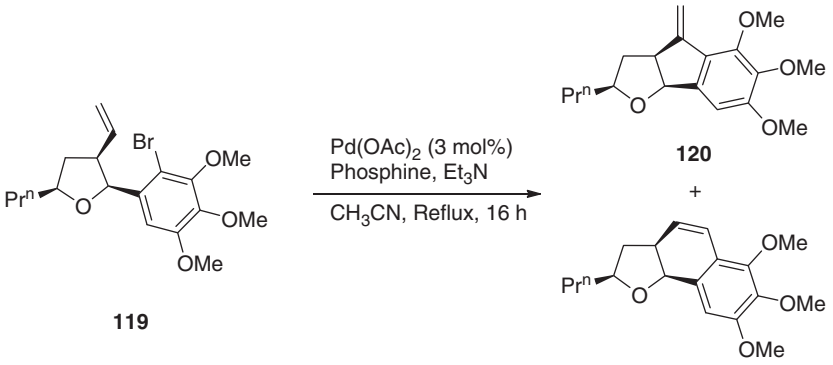
Grigg also used enamide starting materials for the convenient formation of heterocycles.[89] The use of such a substrate allows for the synthesis of cyclic compounds with high stereocontrol. Using Ag salts, the less stable isomer of the product is obtained without isomerization (equation 15).



117 (100% *ee*) (*S*,*S*)-**118** >95% *de* (15)

Electron-rich aryl halides have been used by Marsden in an unusual Heck reaction, forming fused ring systems (Table 8).[90] The cyclization gives the 6-*endo-trig* product, although this is not formed by the 6-*endo-trig* mode of cyclization but by a 5-*exo-trig* mode. It is thought that the nucleophilic substitution at Pd forms a palladacyclobutane, which reductively eliminates to generate a phenonium ion. This fragments and loses a proton to give the 6-*endo-trig* product. As shown by the testing of a similar, unfunctionalized arene, this mode of cyclization occurs because of the electron density of the substrate. The reaction could be tuned to favor either a five- or six-membered ring, depending on the phosphine source (Table 8).

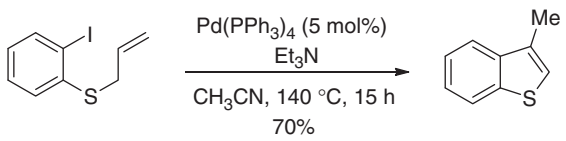
Table 8 Fused ring system formation by a formal 5-*exo* or 6-*endo-trig* reaction



119 **120** **121**

Phosphine	*Equivalent of ligand*	*Yield % (Product)*
dppf	1.9	85 (**120**)
PPh_3	2.0	67 (**121**)

The Heck reaction was also applied to the formation of oxygen- and sulfur-containing heterocycles, a field that developed in the early 2000's. In a similar manner as the formation of indole and indole derivatives,[67] the synthesis of benzofuran derivatives developed by Larock also proceeds via a 5-*exo-trig* pathway followed by second elimination of the readded hydridopalladium species.[73] Although rarely documented, formation of sulfur-containing heterocycles is possible using the Heck reaction. In a reaction mechanism similar to that seen in the formation of benzofuran and indole, benzothiophenes have been synthesized under classical Heck conditions (equation 16).[91]



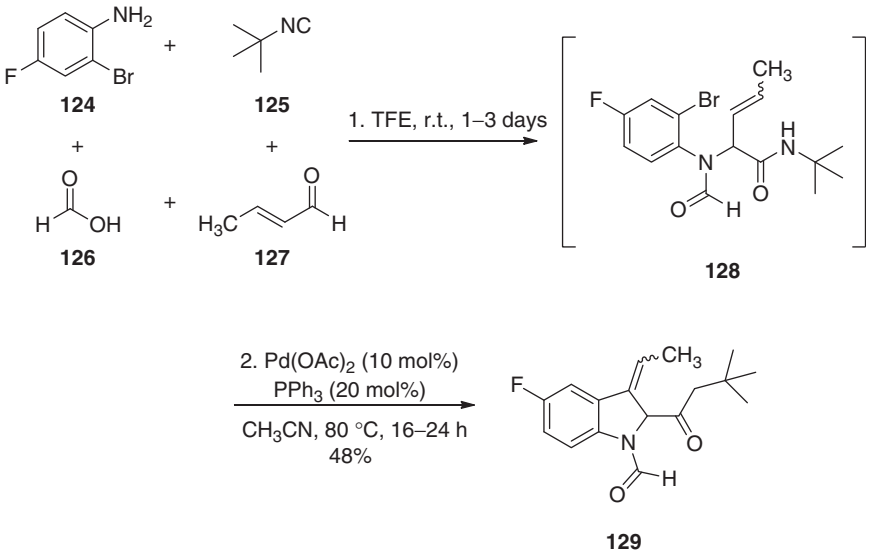
122 **123** (16)

More recently the Heck cyclization has been employed in a multicomponent, one-pot reaction to produce a substrate for the intramolecular Heck reaction.[92] A variety of 2-bromoanilines, acrylic aldehydes, carboxylic acids, and *iso*cyanides were employed in the reaction, ultimately producing indole derivatives that can be further functionalized to give pharmacologically relevant building blocks (Scheme 4).

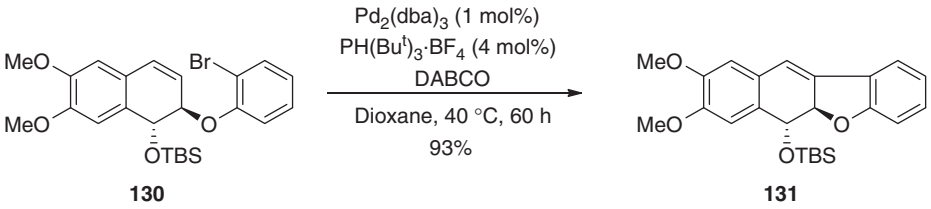
Another interesting Heck cyclization was described by Lautens, in which the elimination of the Pd species after cyclization is by a base-assisted antihydride elimination.[93] This reaction affords the tetracycle (**131**) in a high yield of 93% (equation 17). A large variety of substrates were screened under these reaction conditions and moderate to excellent yields were obtained.

4.14.4.2.2 5-Endo-trig

The 5-*endo-trig* cyclization is unfavored according to the Baldwin rules. The 5-*endo-trig* mode of Heck cyclization is less prevalent than the 5-*exo-trig* mode. Most substrates that undergo this cyclization can also proceed through the 4-*exo-trig* mode of cyclization, a reaction that is favored according to the Baldwin rules. This 4-*exo-trig* reaction will be covered in more detail in Section 4.14.4.3 on small ring formation.

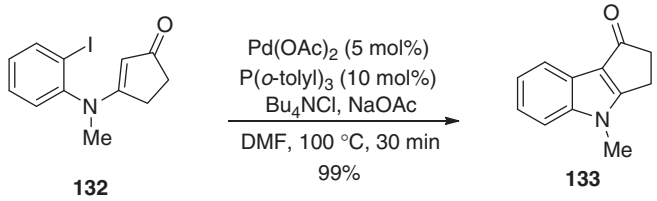


Scheme 4



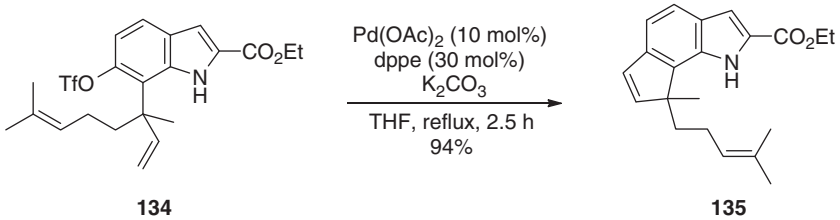
(17)

The 5-*endo-trig* cyclization, like many of the unfavored Baldwin rules, is more prevalent in heterocyclization. Many examples of this heterocycle formation use enaminone-containing starting materials.[94] Sorensen has used enaminone substrates in a MW-assisted tricycle formation, that is fast and quantitative (equation 18).[95]



(18)

Tanner reported a Heck reaction on a substrate possessing two possible sites with the 5-*endo-trig* product being preferentially formed over the 6-*exo-trig* product (equation 19).[96] This is believed to be due to the steric bulk of the quaternary carbon, which is thought to effectively lock the double bond of the starting material in the proximity of the Pd that is oxidatively added, yielding the 5-*endo-trig* product. Also the geometry required for bond formation in this system may prevent its inclusion in the Baldwin rules, invalidating the preference for the 6-*exo-trig* mode of cyclization in this instance.



(19)

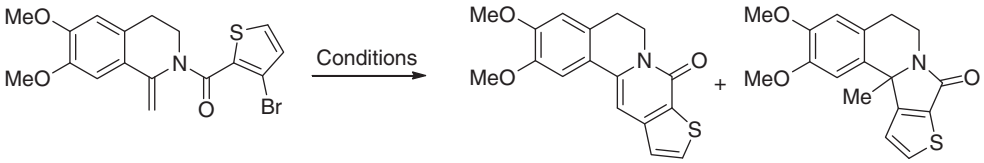
4.14.4.2.3 6-Endo-trig

Similar to the 5-*exo*/*endo-trig* modes of cyclization, the 6-*exo*-cyclization is more favored than the 6-*endo-trig* mode of cyclization. But, as previously stated in Section 4.14.4.2.1 on 5-*exo* cyclization, the 6-*endo* cyclization competes with the 5-*exo* cyclization

mode in most cases. Normally to favor the 6-*endo-trig* mode, the elimination of Pd hydride must be inhibited in the 5-*exo-trig* mode of cyclization.[71a,97]

Sageot has published work on substrates where the 5-*exo-trig* mode of cyclization can dominate by including a hydride source in the reaction conditions.[98] Without this hydride source the 6-*endo-trig* mode is favored (Table 9).

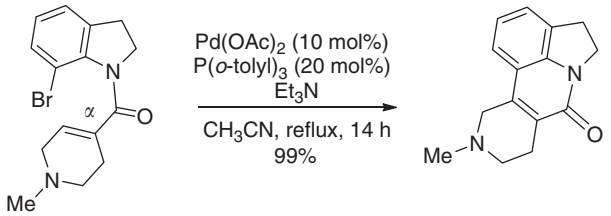
Table 9 Selective 5-*exo*/6-*endo* mode cyclization by variation of reaction conditions



136 **137** **138**

Conditions	*Yield (%)*	***137*:*138***
$Pd(OAc)_2$ (10 mol%), Na_2CO_3, Et_4NCl, DMF	55	99:1
$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), HCO_2H, piperidine	31	>4:96

Exclusive 6-*endo-trig* cyclization has also been reported by Flippin using *N*-acryloyl-7-bromoindolines, which could plausibly cyclize by the 5-*exo-trig* mode.[99] Under standard Heck reaction conditions, using a variety of different substituents on the olefin, the 6-*endo-trig* cyclization occurs without formation of the 5-*exo-trig* product (equation 20). The reaction was found to produce small amounts of the 5-*exo-trig* product when the reaction was done on a short time scale but after additional time this product isomerized to the 6-*endo-trig* product. This occurs by readdition and elimination of Pd hydride. The 5-*exo-trig* mode of cyclization is believed to be disfavored due to the strain involved in the approach of the Pd species to the α-position of the acrylamide double bond.



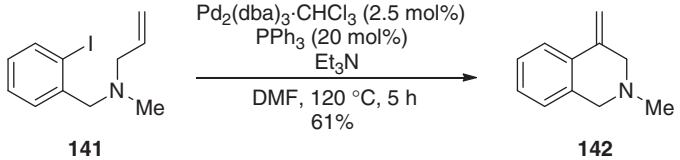
139 **140** (20)

4.14.4.2.4 6-Exo-trig

Development of the 6-*exo-trig* mode of cyclization using the Heck reaction coincided with the 5-*exo-trig* development. This is due to the simple application of the 5-*exo-trig* methodologies to this slightly larger ring size. In many cases, such as those seen in the work by Hallberg on the enamine substrates (Table 7), the 6-*exo-trig* is accessed by the addition of an atom to the chain length of the starting material.

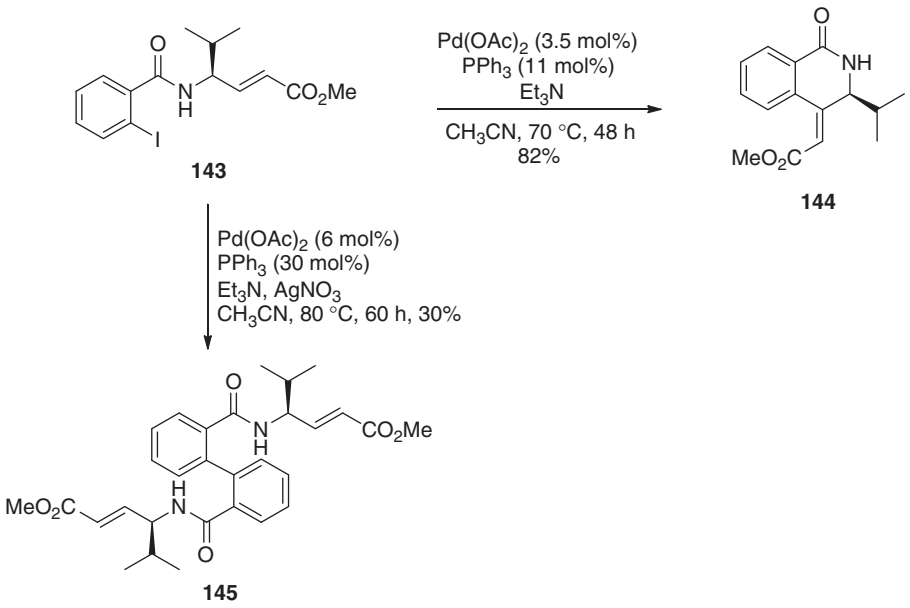
As previously mentioned, *exo* is largely the favored cyclization compared with *endo* and the majority of heterocycles formed are nitrogen-containing, with oxygen- and sulfur-containing ring formations being less prevalent.

In efforts toward the synthesis of isoquinoline derivatives, building on work previously published by Clique,[100] Beccalli formed the less stable *exo*-cyclic product only (equation 21) and the synthesis was applied to spiro[isoquinoline-4,5′-isoxazoles], compounds of pharmaceutical interest.[101]



141 **142** (21)

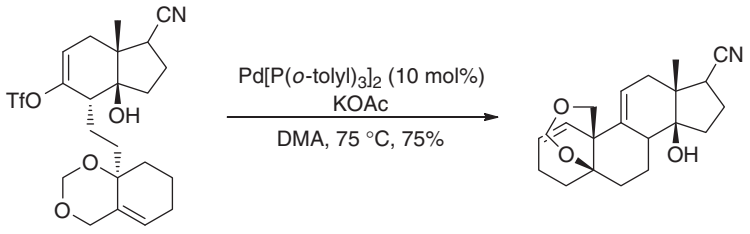
Herradon has found that using the Heck–Overman conditions the biaryl product was solely produced, with recovery of starting materials (Scheme 5).[102] This is believed to be due to the Ag salt, which is thought to promote an oxidative dimerization of the arylpalladium intermediate. Using the Jeffery conditions, the conversion was lowered to 10% over 36 h. The desired product was obtained using the Heck–Overman conditions in the absence of Ag salts. This gave a high yield of the



Scheme 5

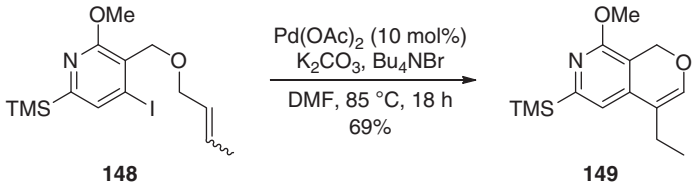
N-(2-*iso*benzoyl)-γ-amino-α,β-unsaturated esters as single regioisomers and stereoisomers. This is an efficient, high yielding synthesis of functionalized chiral heterocycles by the 6-*exo-trig* mode of cyclization.

The synthesis of cardenolide precursors by Overman uses an intramolecular Heck cyclization to form a fused ring system.[103] This step indicates the high functional group tolerance of the Heck reaction, which can be used at a later stage during total synthesis. The reaction also uses a vinyl triflate, a difficult substrate due to its sterically hindered structure, and proceeds with a high yield of 75% (equation 22).



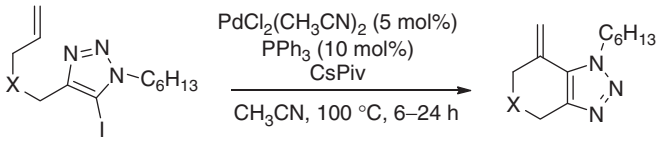
(22)

The prevalence of six-membered oxygen-containing rings in natural products has resulted in a large development in the synthesis of these structures. The synthesis of antitumor agent (20*S*)-camptothecin by Curran uses the conditions developed by Grigg in a high yielding intramolecular late-stage cyclization.[104] The formation of this enol ether (**149**) is a further illustration of the high functional group tolerance of the Heck cyclization (equation 23).



(23)

Lautens has recently reported a 6-*exo-trig* formation of carbocycles and nitrogen- and oxygen-containing rings.[105] This methodology uses 5-iodotriazoles to form 1,2,3-triazole-fused heterocycles. This is of particular interest as a number of triazole-containing compounds are used as chemotherapeutic and cardiovascular agents. A large variety of triazole substituents were tested, all of which gave high yields, a selection of which is given in equation 24.



150a X = O
150b X = NTs
150c X = $C(CO_2Et)_2$

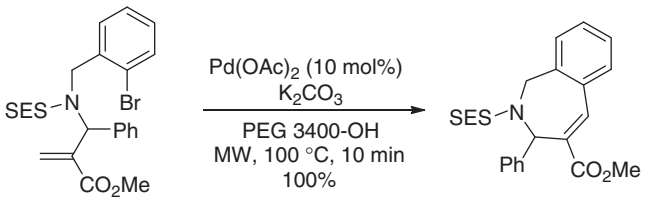
151a (92%)
151b (99%)
151c (89%)

(24)

4.14.4.2.5 7-Endo-trig

Seven-membered rings are less common than the five- or six-membered rings with *endo*- and *exo*-selectivity being almost equally common. The development of seven-membered ring formation using the Heck reaction began later than that for five- and six-membered rings, with most development occurring in the 1990's.

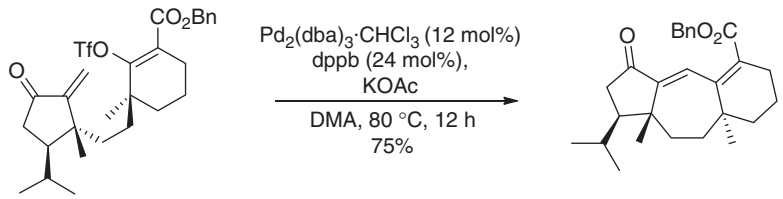
The 7-*endo-trig* mode of cyclization is most commonly seen in the formation of heterocycles such as benzazepines and their derivatives, as these active pharmaceutical agents contain a seven-membered *N*-heterocycle. Declereck has used alkylated SES-protected α-amino esters in a Heck cyclization, generating benzazepines in excellent yields.[106] The reaction requires the use of PEG and is a MW-assisted methodology (equation 25). Under thermal conditions the yield dropped to 23% with recovery of starting material.



152 **153**

(25)

Overman reported a total synthesis of guanacastepene N, a challenging synthetic target with antibacterial activity against MRSA.[107] A 7-*endo* Heck cyclization was used as a pivotal step in this synthesis. The reaction proceeds with 75% yield of the carbocycle (**155**) while maintaining the stable benzyl ester in the product (equation 26).

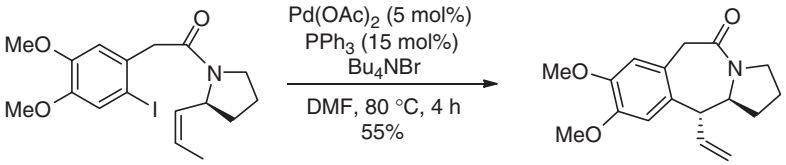


154 **155**

(26)

4.14.4.2.6 7-Exo-trig

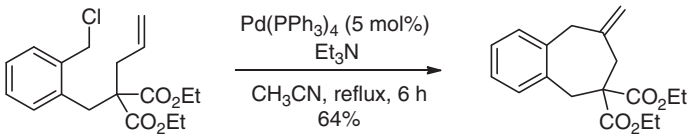
Tietze developed a method of preparing 3-benzazepines, which are benzo-fused seven-membered nitrogen-containing heterocyclic rings of interest due to their sedative effects.[108] An enantiomerically pure heterocycle is produced with high regioselectivity (>30:1), moderate yield (55%) and a diastereoselectivity of 6:1 (equation 27).



156 **157**
dr = 6:1

(27)

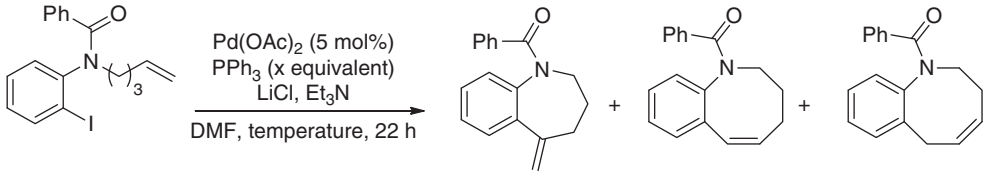
Negishi has worked on the formation of medium sized carbocycles, using benzyl chlorides and catalytic $Pd(PPh_3)_4$ to give products with high retention of the alkene regiochemistry.[81] Focusing on the formation of the seven-membered carbocycle, the regioselectivity was 99% with a high yield of 64% (equation 28).



158 **159** (28)

Hii described the synthesis of benzazepines using the intramolecular Heck reaction.[109] As described by Baldwin rules, the 8-*endo* is less favored than the 7-*exo* and in this case the 7-*exo* product (**161**) is always the dominant mode of cyclization (Table 10). By varying the equivalents of the ligand used the reaction could be tuned to give a higher or lower ratio of 7-*exo*:8-*endo* products.

Table 10 Variation of product distribution in the synthesis of diazepine

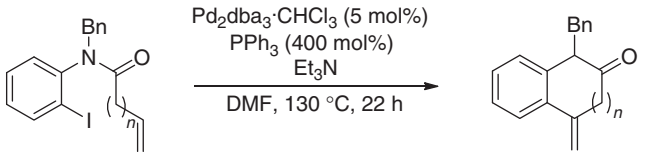


160 **161** **162** **163**

x	*Temperature (°C)*	***161** (%)*	***162* + *163** (%)[a]*
3	120	51	17
4	130	88	0

[a]Inseparable mixture of **162** (Major) and **163** (Minor)

Hii also applied this methodology to the synthesis of benzolactams with possible selective formation of the 7-*exo* or 8-*exo* product depending on the chain length of the starting material (equation 29). High yields were achieved with exocyclic double bonds formed exclusively.



164a $n = 2$
164b $n = 3$

165a $n = 2$, 81%
165b $n = 3$, 79% (29)

4.14.4.3 Small Rings

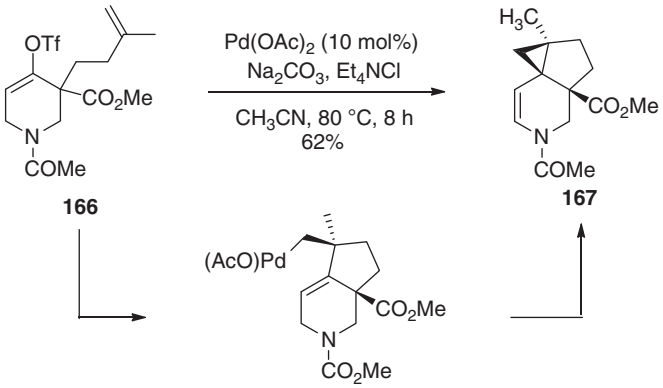
The use of the intramolecular Heck cyclization for the synthesis of small rings is not as well documented as the other ring sizes. The 3-*exo-trig* reaction pathway is favored according to the Baldwin rules, with 3-*endo-trig* being undocumented, probably due to the highly strained intermediates formed during these cyclization modes of the Heck reaction.

4.14.4.3.1 3-Exo-trig

An interesting example of the 3-*exo-trig* pathway was reported by Grigg.[110] The reaction is preceded by a 5-*exo-trig* reaction, generating the double bond that undergoes the 3-*exo-trig* reaction in a domino type process with a high overall yield of 62% (Scheme 6).

4.14.4.3.2 4-Endo-trig

4-*Endo-trig* cyclization is disfavored by the Baldwin rules and formation of a four-membered cyclic structure using this mode in a Heck cyclization appears to be unknown. This is probably due to the strain in the molecule, with the double bond incapable of allowing the correct orientation required for product formation.



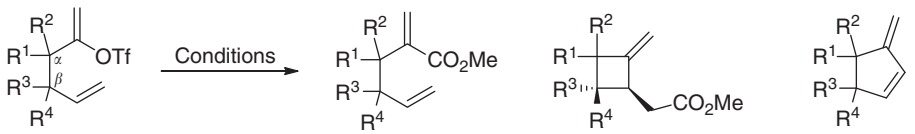
Scheme 6

4.14.4.3.3 *4*-Exo-trig

The 4-*exo-trig* cyclization is favored according to the Baldwin rules. This mode of cyclization can compete with a 5-*endo-trig* mechanism, which is disfavored according to the Baldwin rules. Cyclobutanes pose a synthetic challenge due to the ring strain inherent in the product, with a bond angle of near 90°. The ring strain is approximately 110 kcal/mol, with puckering of the ring reducing the strain slightly.

Mulzer has described a selective 4-*exo-trig* cyclization using the Heck reaction.[111] The substitution of the acyclic starting material is important, as there are various competing reactions (Table 11). 4-*Exo-trig* cyclization, direct carbonylation and 5-*endo-trig* cyclization are all possible reaction pathways in this reaction, all of which can be detected. Selectivity for a particular pathway is possible with variation of the reaction conditions. Making use of the Thorpe–Ingold effect with *gem*-disubstituted quaternary carbons in the substrate the 4-*exo-trig* product is selectively formed (entry ii, iii, iv, v).

Table 11 Variation of the substitution gives varying products



Entry	*Substitution*	***170*** *(%)*	***171*** *(%)*	***172*** *(%)*
i[a]	$R^1=R^3=$Me, $R^2=$OPMP, $R^4=$H	0	25	35
ii[a]	$R^1=R^2=$Ph, $R^3=$Me, $R^4=$H	0	87	0
iii[a]	$R^1=R^2=$Ph, $R^3=$^{i}Pr, $R^4=$H	0	75	0
iv[b]	$R^1=R^2=R^3=$Me, $R^4=$H	3	65	0
v[b]	$R^1=R^2=$Me, $R^3=$^{i}Pr, $R^4=$H	0	65	0
vi[b]	$R^1=$OBn, $R^2=$H, $R^3=R^4=$Me	75	0	0

[a]MeOH/DMF (2:1), $Pd(PPh_3)_4$ (10 mol%), Et_3N, 50 °C, 2–18 h.
[b]MeOH/DMF (2:1), $Pd(PPh_3)_4$ (10 mol%), Et_3N, 50 °C, CO atm, 2–18 h.

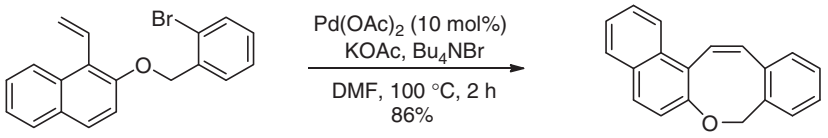
If the substrate is *β*, *β*-disubstituted, the Pd addition appears to be inhibited from approaching the second olefin as it attempts to avoid the steric hindrance of the R^4 substituent and so the acyclic product is favored (entry vi). Using an ether substituent in the *α*-carbon, there is considerable preference for the 5-*endo-trig* product as the cyclobutane–organopalladium intermediate has an extended lifetime (entry i). It was also found that the absence of a CO atmosphere produced an excellent yield of the cyclobutane product selectively (entry ii, iii).

4.14.4.4 Large Rings

As the ring size increases the preference for the *endo* mode of cyclization increases. This is due to the more flexible tether in these larger rings, generating a more energetically favorable transition state for *endo*, which is not possible for smaller ring sizes. A large number of these syntheses are performed using solid supports.

4.14.4.4.1 8-Endo-Trig

Sinha has studied the selective formation of cyclized oxocine derivatives by an 8-*endo-trig* mode of cyclization.[112] After optimization of the reaction, a number of substrates could be employed in this reaction to afford high yields of this 8-*endo*-cyclized product as the *Z*-isomer only (equation 30).

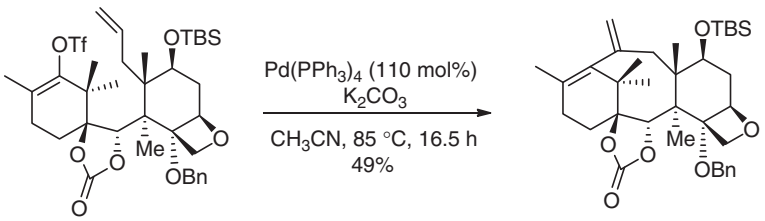


173 **174** (30)

4.14.4.4.2 8-Exo-Trig

As previously discussed in Section 4.14.4.2.6 on 7-*exo-trig* cyclization, the 8-*exo* cyclization is possible using conditions shown in equation 29.[113] It was found that under these conditions, the eight-membered benzazocine ring forms in a high yield because the rigidity of the acyclic chain induced by the amide moiety. This results in a reduction in entropy and so leads to a favorable 8-*exo*-mode of cyclization.

Danishefsky developed the 8-*exo*-mode of cyclization to form the B-ring of the Taxol core structure.[114] This late-stage cyclization proceeds with a moderate yield, using an unusually high loading of Pd (equation 31).



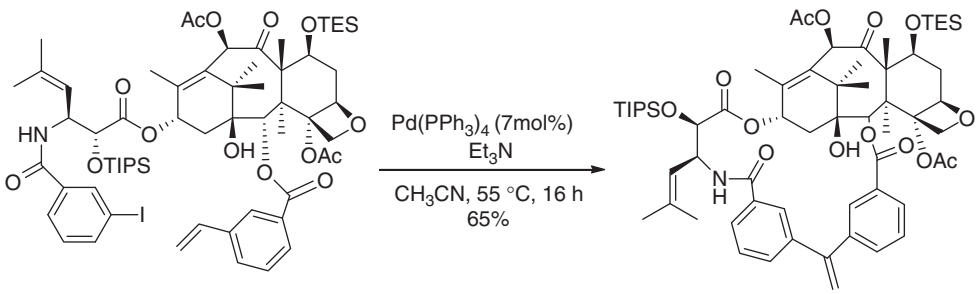
175 **176** (31)

4.14.4.5 Macrocyclization

Macrocycles are often encountered in natural products, and the Heck reaction is one of the few methods of preparing such compounds. Many of these cyclizations are conducted in highly dilute systems or on solid support. The regioisomer selectivity and the side-products are difficult to control in such ring formations. There are often side-products encountered in these steps as they are performed at a late stage in synthesis, after building up much functionality on the macromolecule.

Ziegler was the first to report the heterocyclic macrocyclization and like many other macrocyclizations, the yields were moderate.[115] The reaction has since been used to synthesize biologically important compounds such as steroids, including the formation of a 13-membered carbocyclic steroid skeleton by Dyker.[116]

Another interesting use of the Heck cyclization is the synthesis of macrocyclic taxoids by Ojima.[117] An intramolecular Heck reaction is a key step in this synthesis. The reaction proceeds with a high yield of 65% and only produces the required *exo*-cyclized product (equation 32).



177 **178** (32)

4.14.4.6 Conclusion

As can be seen in the discussion above, the development of the Heck-based cyclization has been ongoing since the 1970's. Development in the reaction methodology has allowed for a wide breadth of substrates to be used in the formation of rings, from three-membered rings to macrocycles. This methodology has allowed the formation of carbocycles and heterocycles, including nitrogen-, oxygen-, and sulfur-containing rings. The yields of these reactions have increased as the reaction conditions have evolved. Also, the regio- and stereoselectivity can be tuned to give a variety of products. A key feature of this Heck cyclization is its high functional group tolerance. The use of the reaction for late-stage cyclization in total syntheses of complex molecules supports this and also shows the wide application of this reaction.

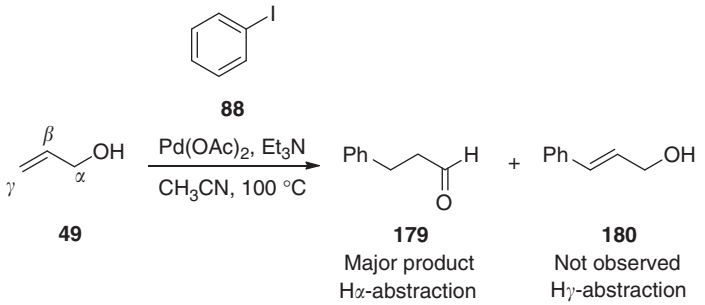
4.14.5 Chelation Control

Chelation control in the Heck reaction leads to the introduction of stereo- and regioselectivity by coordination of a heteroatom on the substrate to the palladium catalyst in the carbopalladation step, promoting an intramolecular-type reaction. Hallberg was the first to introduce this concept to the Heck reaction, thus greatly improving its utility and efficiency.[118]

4.14.5.1 Reaction Development

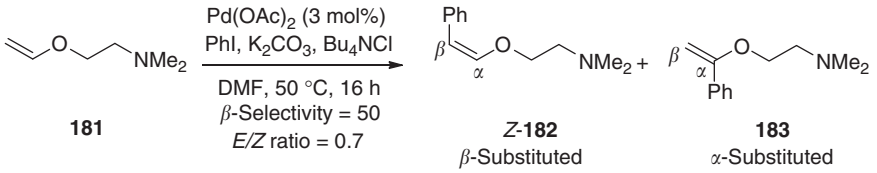
4.14.5.1.1 Regioselectivity induction in vinyl ethers

In the original reaction of allylic alcohols, β-elimination afforded 3-phenylpropanal, with H-abstraction occurring primarily in the α-position,[320] with no γ-elimination product forming (equation 33). Hallberg addressed the issue of regioselectivity in the Heck reaction using a series of nitrogen heteroatom-containing vinyl ethers, originally considered elusive substrates for the Heck reaction.[118]



(33)

They demonstrated that substrate control profoundly influenced the regioselectivity in the arylation of such vinyl ethers. The use of a coordinating group allowed for the intramolecular delivery of the aryl fragment and so mimicked an intramolecular reaction. Using easily available β-amino substituted vinyl ethyl ethers, traditional Heck reaction conditions afforded a significant increase in β-selectivity.[118] The use of phase-transfer conditions allowed the reaction to be run in the absence of competing trialkylamine, affording an increased β-selectivity of 50 (equation 34).

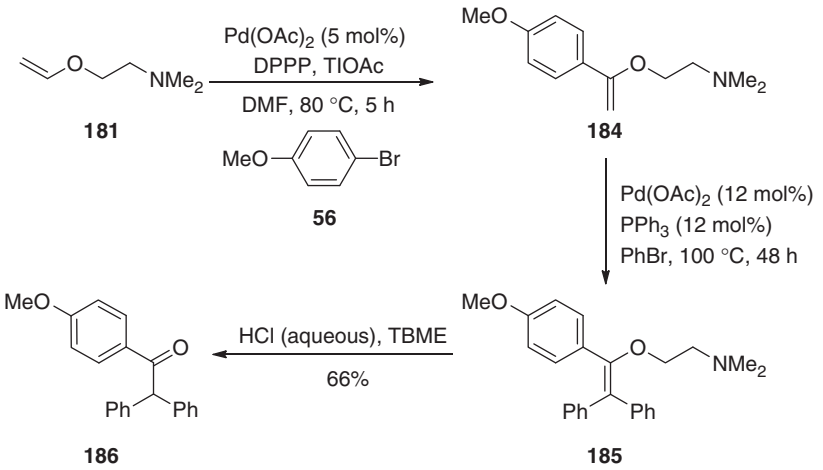


(34)

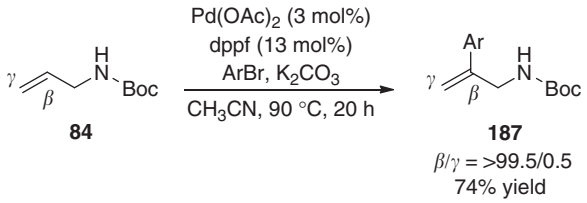
Exploratory studies conducted by Hallberg indicated formation of a chelated organopalladium intermediate, which resulted in inherent regioselectivity for vinyl ethers being completely suppressed by the chelation of the β-amino substituent.

This methodology was later applied by Hallberg to develop a Heck triarylation process.[119] This novel Heck reaction involves chelation control with intramolecular presentation of the oxidative addition complex. Simple diethyl amine vinyl ethers were used to synthesize α,β,β-substituted ketones using various aryl bromides in moderate to good yields of up to 66% after hydrolysis (Scheme 7).

The synthesis of internally arylated allylamines in a one-step reaction procedure was also studied by Hallberg.[120] Efficient coordination of the anionic nitrogen of the Boc-protected allylamide to the cationic Pd generated an energetically favored penta-coordinated π-complex intermediate. Subsequent β-hydride elimination is regioselective for β- over γ-substitution with selectivities of greater than 99.5:0.5 and isolated yields of up to 74% (equation 35).



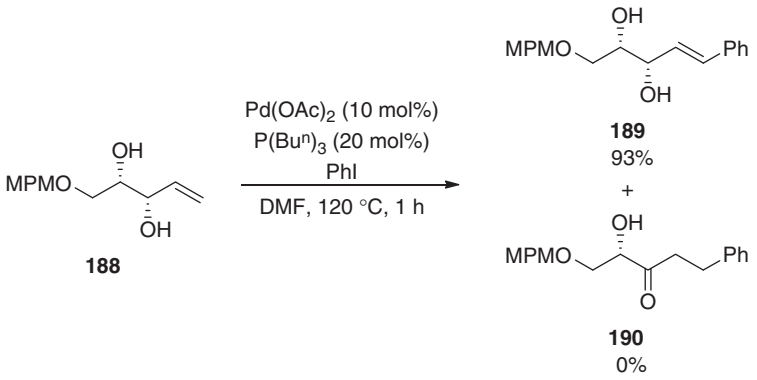
Scheme 7



(35)

4.14.5.1.2 Regioselectivity induction in allylic diols

Kim reported the use of allylic diols as chelating substrates for the highly selective synthesis of phenyl-substituted allylic diols.[121] A four-membered intermediate is assumed, making the hydrogen on the hydroxy bearing carbon unfavored for β-hydride elimination. This work built on that published by Tamaru using oxygen-substituted allylic alcohols as a directing group for coupling.[122] α,β-Unsaturated diols can be synthesized from aromatic halides and allylic diols using mild conditions and nonamide bases affording yields of up to 93%, with suppressed formation of the β-aromatic hydroxy carbonyl product (equation 36).



(36)

4.14.5.2 Asymmetric and Stereoselective Reactions

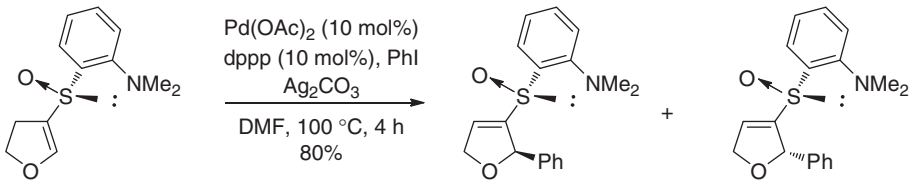
Removable or functionalizable chelating groups are often used to achieve a stereoselective Heck reaction when an existing functional group within the substrate is unsuitable. These groups can then be removed or further transformed to generate complex molecules.

4.14.5.2.1 Stereoselectivity induction by sulfoxides and sulfides

Carretero[123] was the first to apply chiral auxiliaries to the Heck reaction to control the stereoselectivity of the reaction. Sulfoxides had previously been used as chiral auxiliaries in asymmetric synthesis,[124] but their use in asymmetric transition metal-catalyzed reactions as a directing group was novel.

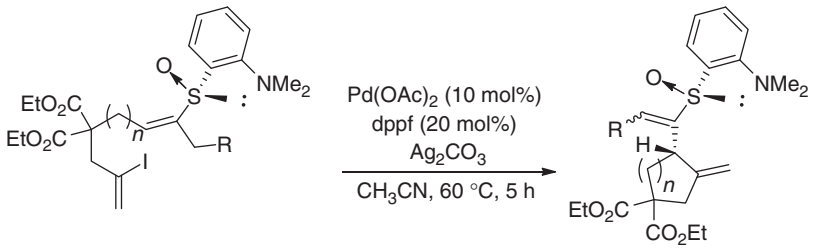
4.14.5.2.1.1 Dimethylamino sulfoxide as the chiral auxiliary

Carretero used *o*-dimethylamino sulfoxide to produce 2-aryl-3-sulfinyl-2,5-dihydrofurans with a high level of stereocontrol. It was postulated to be directed by steric or chelating effects of the nitrogen of the sulfinyl group during the insertion step affording up to 88% diastereomeric excess (equation 37).



191 → **192** 6 : **193** 94 (37)

Subsequently Carretero further developed the scope of this asymmetric methodology, allowing the use of this chiral chelating group in the intramolecular reaction of 2-iodo-1,6 (or 1,7) dienes to afford the corresponding exocyclic alkenes (equation 38).[125]



194a R = Me, *n* = 1
194b R = H, *n* = 2

→ **195a** (70% mix of *E*:*Z* 5:1)
195a (61%)
>96% *ee* (38)

Carretero also used this directing group for the asymmetric synthesis of (2*R*)-2-phenyl-2,5-dihydrofuran (**196**) and (2*S*, 4*R*)-2,4-diphenyltetrahydrofuran (**198**), with excellent enantiopurity of greater than 96% after removal of the chelating group (Scheme 8).[9,126]

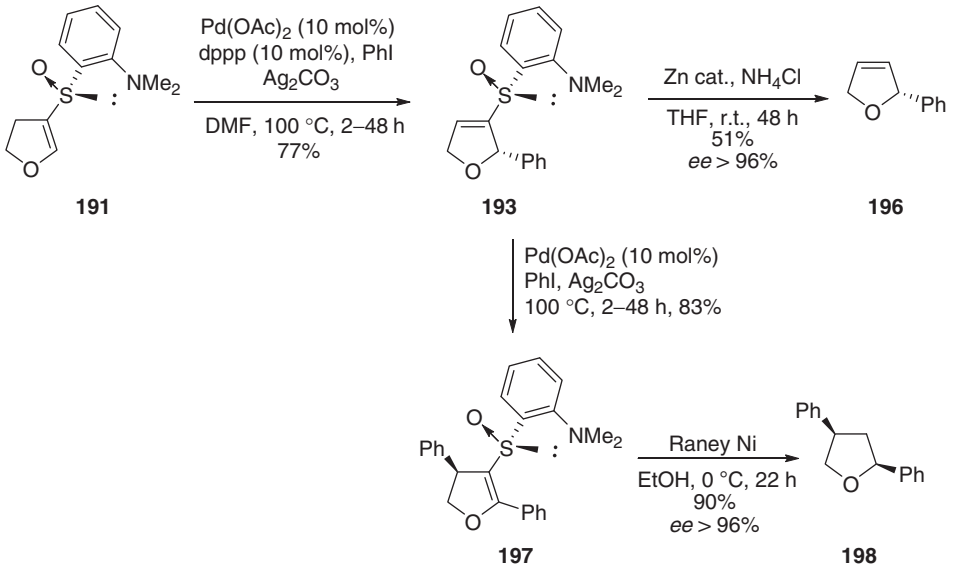
4.14.5.2.2 2-Pyrimidyl sulfide as the directing group

Vinyl sulfides were previously known to have low reactivity in the Heck reaction but adding the 2-pyrimidyl group on sulfur was shown by Yoshira to increase the reactivity of the vinyl sulfide toward the Heck reaction.[12,127,128] Using a $Pd[P(Bu^t)_3]_2$ catalytic system it was possible to achieve a one-pot installation of two aryl groups at the *β*-carbon, a reaction that was previously hard to achieve (Table 12).

The chelating pyrimidyl group can subsequently be replaced by an aryl group using a cross-coupling reaction with aryl Grignard reagents. By addition of the components of the reaction in a sequential manner the substitution and regioselectivity can be controlled to give all regio- and stereoisomers of these tetra-substituted olefins in high yields (Scheme 9).

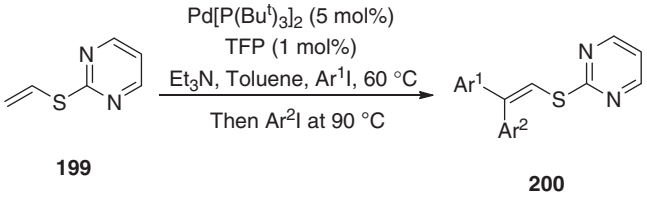
4.14.5.2.3 Stereoselectivity induction using prolinol

More recent developments in chelation control of the Heck reaction have involved the use of a prolinol group possessing a chiral tertiary-amine containing unit to direct the diastereotopicity of insertion in prolinol vinyl ether.[129] Acid-mediated hydrolysis of the product ether generates enantiomerically enriched cyclopentanones with 90–98% *ee*. Larhed expanded the scope of this prolinol chelation controlled intermolecular Heck reaction to include aryl chlorides, vinyl chlorides, vinyl triflates, and vinyl bromides.[130,131] These chiral pyrrolidine-based vinyl ethers afforded quaternary 2-aryl/vinyl-2-methyl cyclopentanones in 90–98% *ee* (Table 13).



Scheme 8

Table 12 Heck reaction of vinyl 2-pyrimidyl sulfide



Ar^1	Ar^2	Yield (%)
Phenyl	Phenyl	93
1-Naphthyl	1-Naphthyl	95
4-Me-phenyl	Phenyl	94
3-Thienyl	4-MeO-phenyl	94

[a]Reaction performed at 80 °C with 2.0 equivalents of aryl iodides.

The development of chiral auxiliary-based chelation control showed an alternative to the use of chiral ligands for the induction of asymmetry in the Heck reaction (*vide supra*). Many of the chelating groups can also be used in further synthetic transformations to generate highly complex compounds.

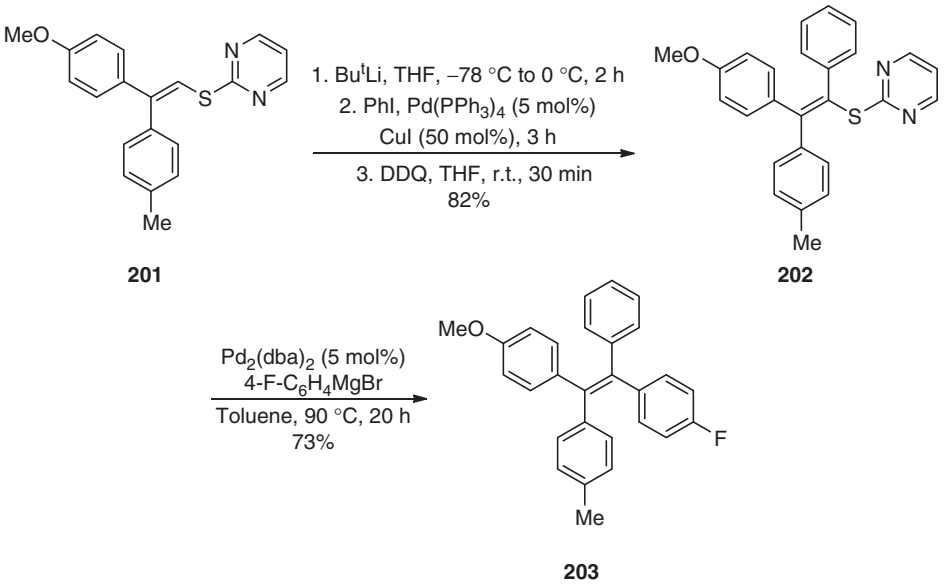
4.14.6 Domino/Cascade/Tandem Processes Involving the Heck Reaction

4.14.6.1 Introduction

The ability to carry out a number of organic transformations in the same reaction vessel without the need to isolate intermediates and vary reaction conditions offers the possibility to greatly improve the efficiency of an organic synthetic sequence. One way of achieving this is via domino reactions, sometimes referred to as cascade reactions; both are a form of tandem reactions. As defined by Tietze, a domino reaction is a 'process involving two or more bond-forming reactions under identical reaction conditions, and in which the latter transformations take place at the functionalities obtained in the former bond-forming reactions.'[132] Due to the ability of Pd to tolerate a large variety of functional groups, it is an ideal catalyst for domino processes. This section will focus on domino reactions incorporating a Heck or Heck-type coupling.

4.14.6.2 Heck/Heck-Domino Reactions

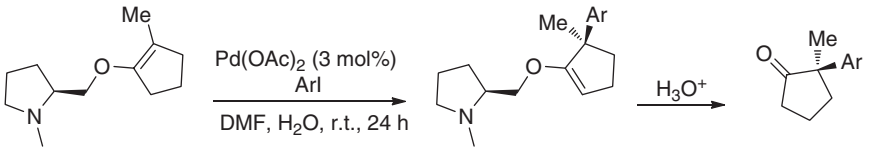
De Meijere and coworkers reported a Pd-catalyzed domino tetracyclization sequence via two-consecutive intramolecular Heck reactions followed by a subsequent 6π electrocyclization.[133] This cascade cyclization–cyclopropanation sequence was originally



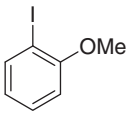
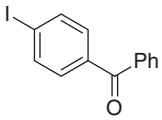
201 **202** **203**

Scheme 9

Table 13 Chelation control asymmetric arylation of prolinol vinyl ether



204 **205** **206**

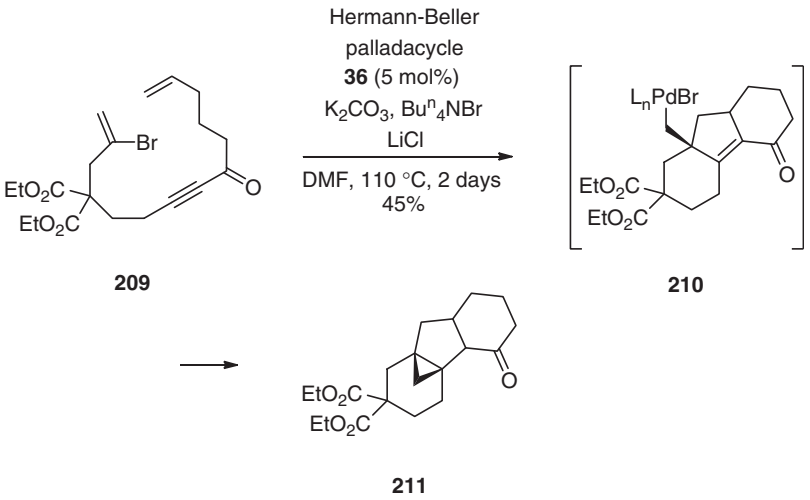
ArI	*Temperature (°C)*	*Yield % **206***	*ee % **206***
 **207**	70	67	98
 **208**	80	47	97

developed by Grigg and expanded by de Meijere to form four new rings and four new C–C bonds in one reaction starting from bromodienyne **209**, which forms alkyl Pd intermediate **210** which undergoes a final cyclopropanation to form **211** in 45% yield using the Hermann–Beller palladacycle **36** (Figure 8; Scheme 10).[134]

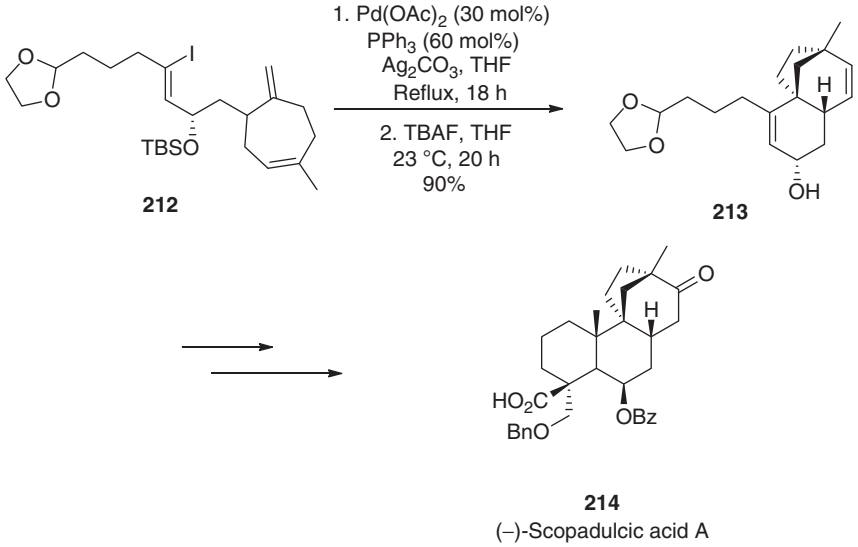
Overman utilized a domino Heck reaction of a methylenecycloheptene iodide to create three rings of the bioactive natural product (–)-scopadulcic acid A.[135] The bis-Heck cyclization takes place with complete regio- and diastereoselectivity in the presence of a high Pd loading of 30 mol% (Scheme 11).

4.14.6.3 Heck/Suzuki and Suzuki/Heck-Domino Reactions

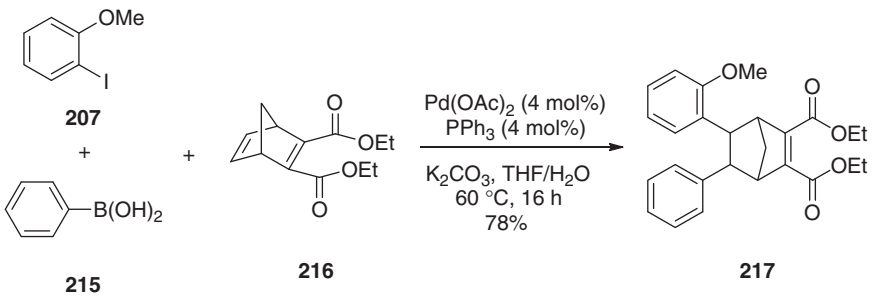
A domino Heck/Suzuki coupling reaction was developed by Goodson and coworkers in the synthesis of diarylnorbornene compounds in yields up to 78%.[136] The reaction of 2-iodoanisole **207** with phenyl boronic acid **215** and norbornadiene diester **216** proceeded via an initial Heck-coupling followed by a Suzuki-coupling (equation 39).



Scheme 10



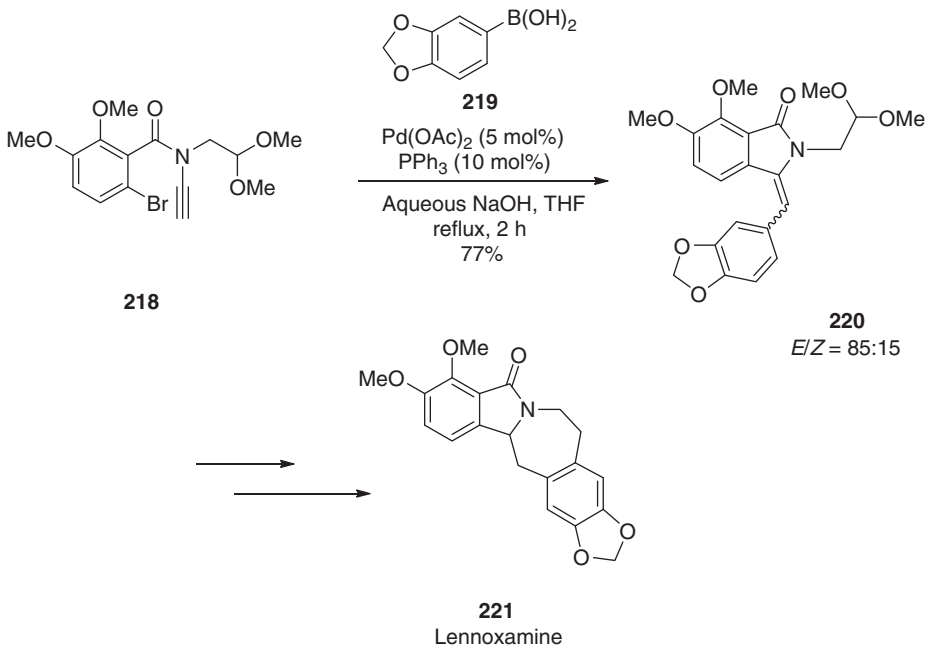
Scheme 11



(39)

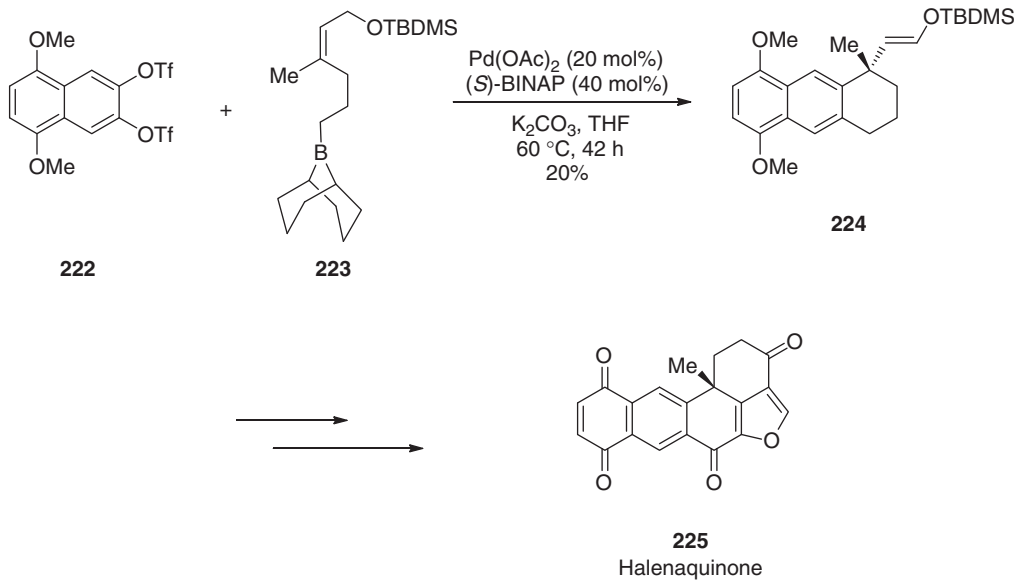
A domino Heck/Suzuki process was utilized by Cossy in the total synthesis of a benzazepine alkaloid lennoxamine (**221**).[137] In the presence of $Pd(OAc)_2$, PPh_3, and aryl boronic acid **219**, the terminal ynamide **218** undergoes an intramolecular Heck reaction to form the isoindolinone structure, followed by a Suzuki coupling on the vinyl Pd intermediate to give **220** (Scheme 12). A similar strategy has also been applied by others and includes a carbonylation before the Suzuki coupling.[138]

The reverse type process has also been described, beginning with a Suzuki reaction. An example was reported by Shibasaki in the synthesis of halenaquinone, albeit in a low chemical yield of 20% (later improved using $AsPh_3$ as a coligand) and *ee* of 85%



Scheme 12

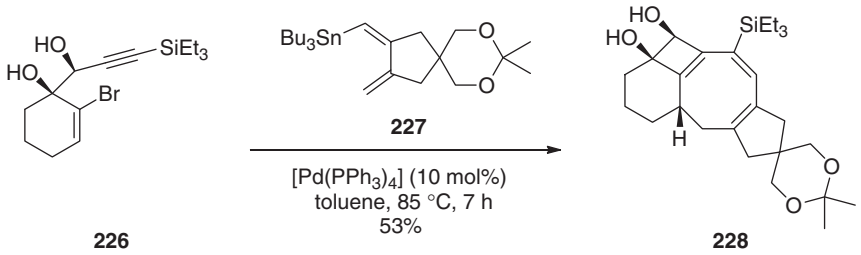
(Scheme 13).[139] De Meijere also reported a Suzuki/Heck domino strategy for the synthesis of polycyclic aromatic hydrocarbons.[140]



Scheme 13

4.14.6.4 Heck/Stille-Domino Reactions

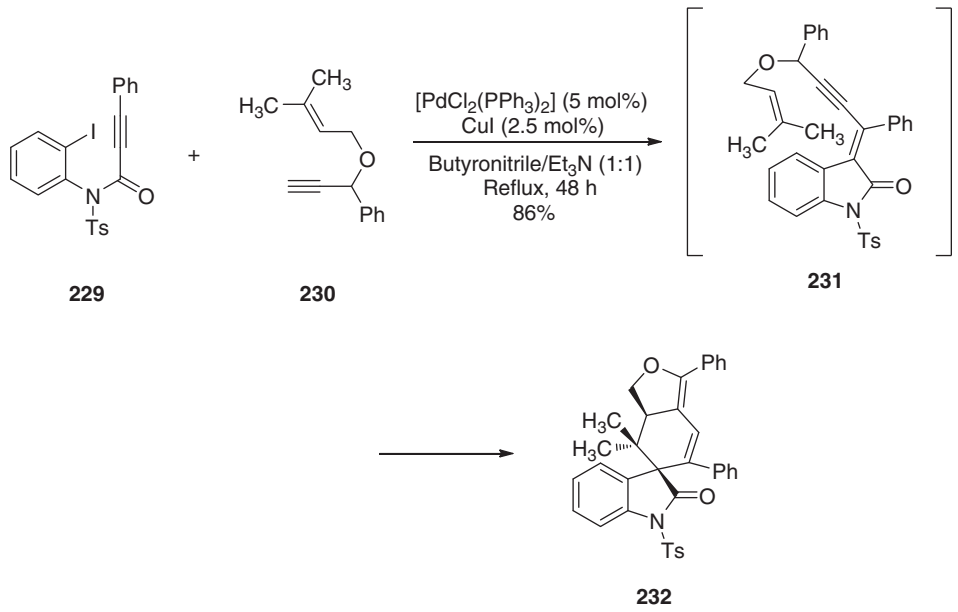
An interesting domino Heck/Stille reaction sequence, reported by Suffert, consisted of an initial Heck reaction followed by a Stille coupling and finally a conrotatory 8π electrocyclization to form highly functionalized tetracyclic compounds.[141] This sequence allowed access to 5,8,5- and 6,4,8,5-polycyclic systems in moderate yields. The most effective substrates were diol **226** and dienyl stannane **227** to yield tetracycle **228** in a 53% yield (equation 40).



226 228 (40)

4.14.6.5 Heck/Sonogashira-Domino Reactions

An interesting example of a domino Heck/Sonogashira process was reported by Müller to afford a new class of spirocycles after a final Diels–Alder [4 + 2] cycloaddition.[142] Initial oxidative addition and *syn*-carbopalladation to the alkyne formed the cyclized vinyl Pd intermediate. Subsequent Sonogashira coupling of the Cu-acetylide leads to the formation of vinylpropargyl allyl ether **231**, which isomerizes to an enallene. This then undergoes a [4 + 2] cycloaddition to form spirocyclic benzofuranones and dihydroindolones in yields of 33–86% (see representative example Scheme 14).



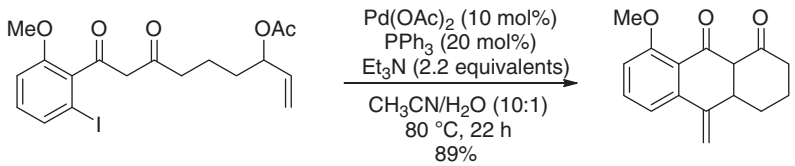
229 230 231 232

Scheme 14

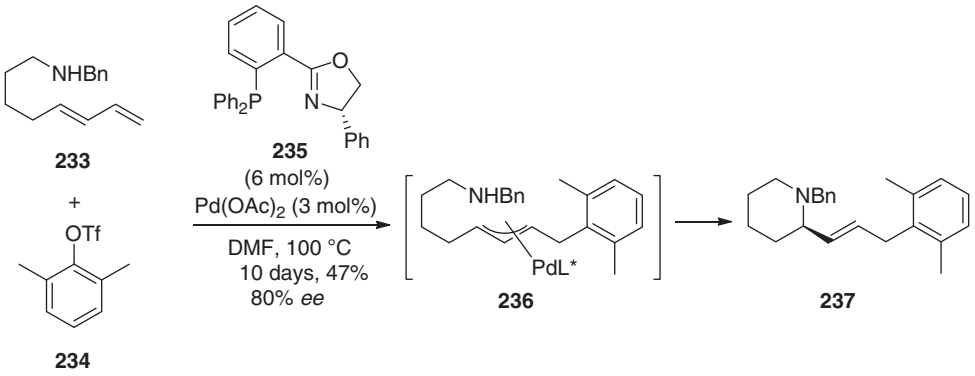
4.14.6.6 Heck/Tsuji–Trost and Tsuji–Trost/Heck-Domino Reactions

The nucleophilic substitution of π-allyl Pd intermediates formed by a Heck carbopalladation has been reported.[143] An asymmetric version of a domino Heck/allylic amination was reported by Helmchen using a diphenylphosphino oxazoline (PHOX) ligand. The initial Heck-arylation generated an allyl Pd complex **236** with the PHOX ligand and the subsequent cyclization occurred with up to 80% *ee* (Scheme 15).[144]

The reverse domino process with the first step as a Tsuji–Trost reaction has also been described in the synthesis of tetrahydroanthracenes by Tietze (equation 41).[145]



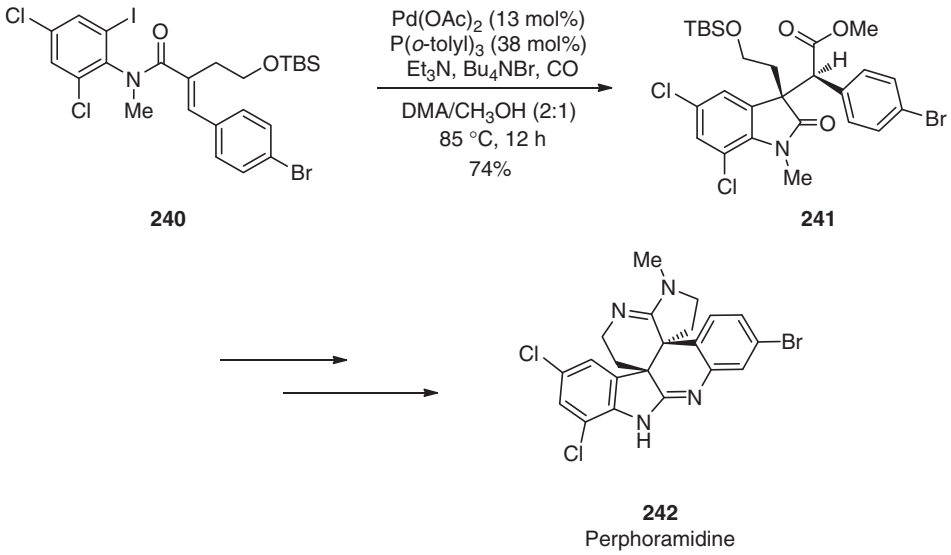
238 239 (41)



Scheme 15

4.14.6.7 Heck/CO-Insertion-Domino Reactions

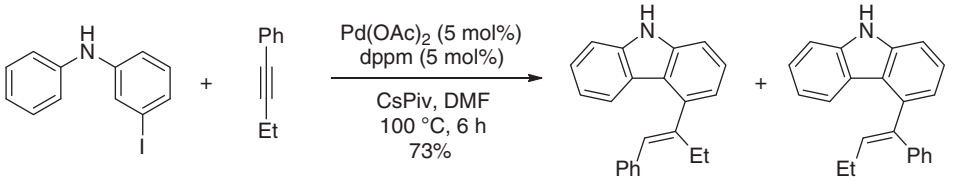
The insertion of CO into organopalladium intermediates is an attractive terminating process for the formation of carbonyl derivatives and thus it has been applied in domino processes beginning with a Heck reaction.[146] A representative example was described by Weinreb in his efforts toward a total synthesis of the marine natural product, perophoramidine. Intramolecular Heck cyclization of the aryl iodide **240** formed the lactam and subsequent CO insertion in the presence of MeOH generated the methyl ester **241** (Scheme 16). In this process two C–C bonds and a quaternary carbon center are generated in a yield of 74%, whereas the aryl bromide and chloride bonds are left intact.[147]



Scheme 16

4.14.6.8 Heck/C–H Activation-Domino Reactions

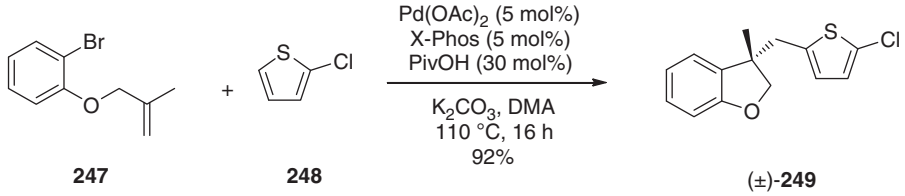
Pd-catalyzed C–H activation has become increasingly popular over the last number of years and, as a result, Heck-coupling reactions have been combined with C–H activations. If the organopalladium intermediate, following Heck coupling, is proximal to an aryl/vinyl hydrogen, activation of this C–H bond by insertion of Pd can occur. This can then undergo further reactions with nucleophiles or electrophiles to form new carbon–carbon/heteroatom bonds. Larock reported the synthesis of carbazoles via a domino Heck/C–H activation sequence. The reaction occurs by carbopalladation of the alkyne **244**, C–H activation by migration of the vinyl Pd intermediate into an aryl C–H bond followed by a second aryl C–H activation and subsequent ring-closure (equation 42).[148] It is believed the simultaneous Pd migration/aryl C–H activation is selective for the C–H *ortho* to the N due to pre-coordination of Pd to N.



243 **244** **245** : **246**
10 : 1

(42)

A domino Heck/intermolecular direct arylation by C–H activation was developed by Fagnou, accessing a route to dihydrobenzofurans, indolines, and oxindoles, substituted with sulfur-containing heterocycles in yields of 41–99%.[149] As an example, the synthesis of dihydrobenzofuran **249** was carried out in 92% yield via an intramolecular Heck-cyclization of aryl bromide **247** followed by intermolecular C–H activation and arylation with 2-chlorothiophene **248** (equation 43).

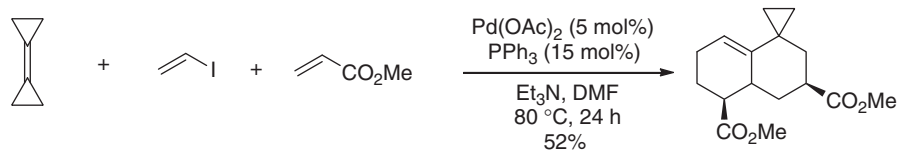


247 **248** (±)-**249**

(43)

4.14.6.9 Heck/Pericyclic-Domino Reactions

The most common domino process involving a Heck reaction followed by a non-Pd catalyzed transformation is with pericyclic reactions, in particular Diels–Alder reactions. This is due to the ease of diene formation as the product of the Heck reaction and, as a result, these processes have been very well studied recently along with other domino Heck/pericyclic transformations.[141b,150] The group of de Meijere has been prominent in this regard and an example is their synthesis of spirocyclopropanated compounds (equation 44).[150a]



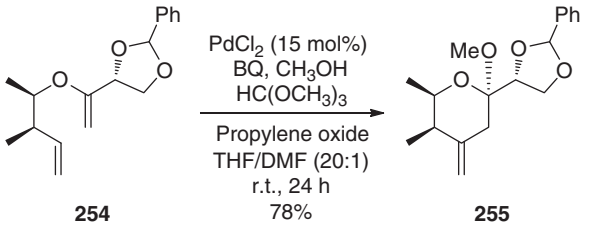
250 **251** **252** (±)-**253**

(44)

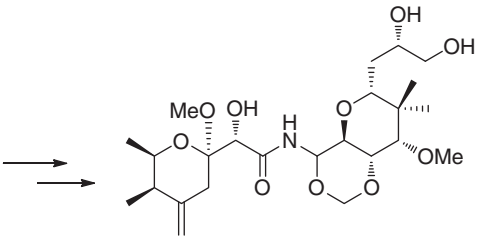
4.14.6.10 Heck/Wacker Oxidation or Wacker Oxidation/Heck-Domino Reactions

The Wacker process is the oxidation of olefins using Pd(II) catalysis and is the most important industrial example of Pd(II) catalysis to produce acetaldehyde from ethylene and water. This transformation has also been applied in a number of domino processes with the Heck reaction. Rawal devised a tandem cyclization sequence from an intramolecular Heck reaction and sequential Wacker-type reaction in a diastereoselective manner in a total synthesis of mycalamine A **256** (Scheme 17).[151]

Tietze utilized an enantioselective domino Wacker/Heck reaction to form the central chromanone unit in the synthesis of 4-dehydroxydiversonal **260** employing a BOXAX ligand **258** (Scheme 18).[152] A tandem Pd(II) catalyzed enantioselective oxidative cyclization using (–)-sparteine as the chiral ligand. This aza-Wacker/Heck process led to the synthesis of indolines in up to 91% *ee* and yields of 63% (equation 45).[153]

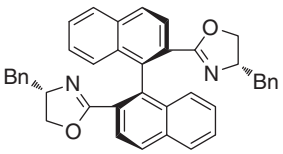


254 **255**

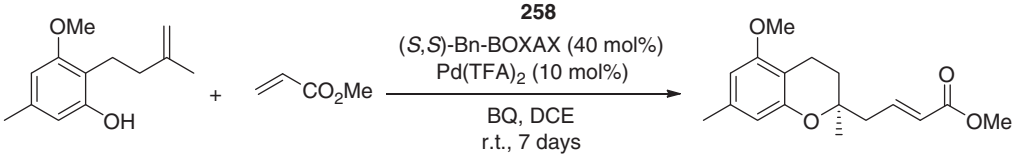


256
Myclamine A

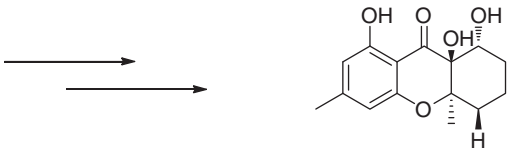
Scheme 17



258

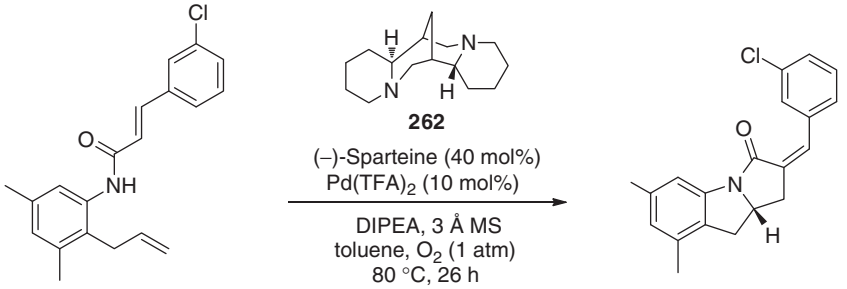


257 **252** **259**



260
4-Dehydroxydiversonal

Scheme 18

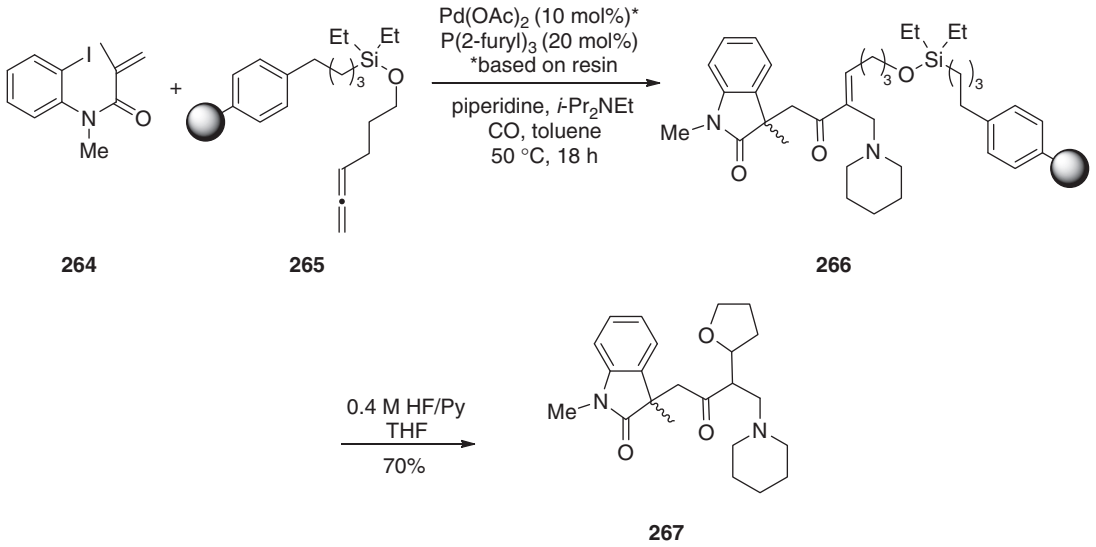


261 **262** **263**

(45)

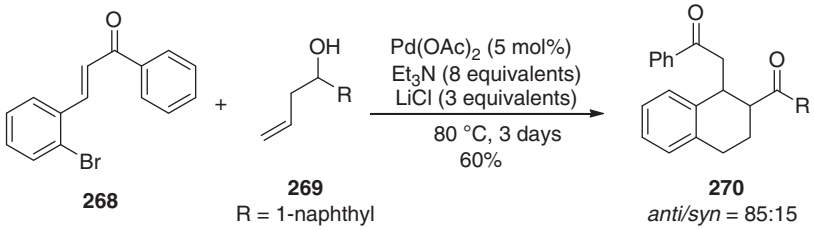
4.14.6.11 Other Heck-containing Domino Processes

An organopalladium intermediate generated from a Heck-coupling reaction can by attacked by an adjacent anion to introduce further complexity in the molecule. A number of examples have been reported[154] and the first was by Grigg in which a polymer-bound allene reacted with an aryl iodide following a CO insertion to form a π-allyl Pd(II) complex which was then captured by a secondary amine (Scheme 19).[155]



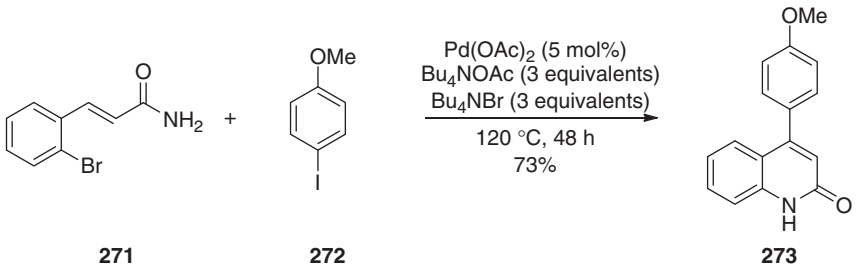
Scheme 19

A Heck reaction can also be followed by an intramolecular aldol or Michael reaction. Both were reported by Dyker and, as an example, the initial Heck coupling of aryl bromide **268** with homoallylic alcohol **269**, was followed by an intramolecular Michael addition to afford the 1,2-disubstituted tetrahydronaphthalene **270** (equation 46).[156]



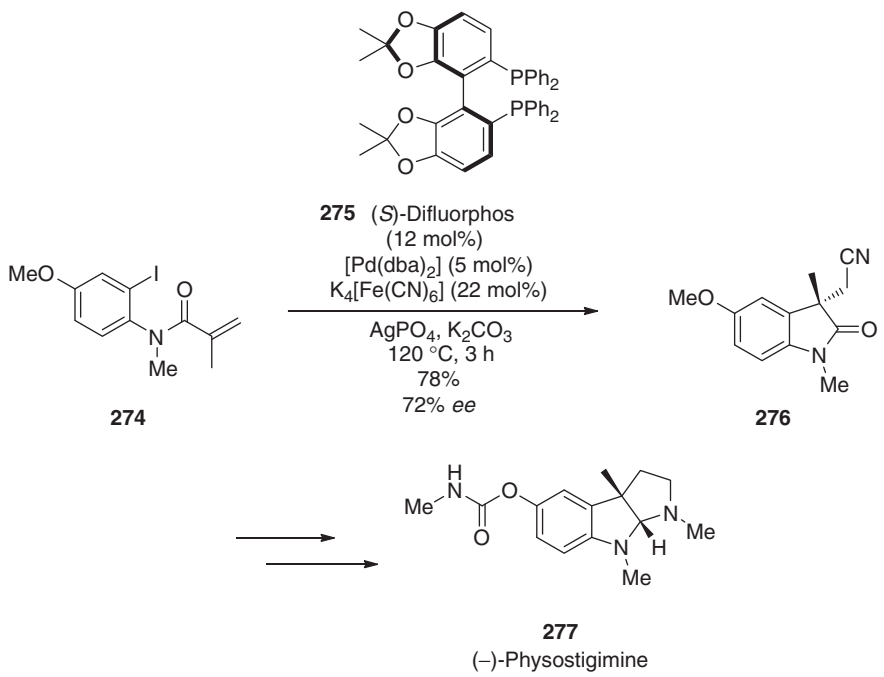
(46)

A domino Heck/Buchwald–Hartwig sequence was reported by Cacchi in the synthesis of 4-aryl-2-quinolones in IL via arylation of acrylamide **271** followed by an intramolecular aryl amination (equation 47).[157]



(47)

An enantioselective domino Heck/cyanation sequence was outlined by Zhu in the total synthesis of physostigmine, another example of an anion capture approach (Scheme 20).[158]



Scheme 20

4.14.7 Oxidative Heck-Type Reactions

The Heck reactions described in Sections 4.14.1–4.14.6 all involve the reaction between an alkene and an aryl/vinyl halide catalyzed by a Pd(0) species. The oxidative Heck reaction however is different in that it evokes the use of a Pd(II) catalyst to couple an alkene with an unfunctionalized arene (Fujiwara–Moritani) or with a functionalized boronic acid.

4.14.7.1 Introduction to the Fujiwara–Moritani Reaction

The Fujiwara–Moritani oxidative Heck reaction involves C–H activation. This is an extremely advantageous approach to the formation of C–C bonds, as it eliminates the need for prefunctionalization of aryl/alky substrates with a (pseudo)halogen. This is especially desirable for industrial applications due to atom economy.

4.14.7.2 Initial Development of the Fujiwara–Moritani Reaction

This oxidative Heck reaction was first observed by Fujiwara and Moritani in 1967.[159] During an investigation into the reaction between styrene and a Pd(II) complex in the presence of acetic acid they isolated stilbene. This reaction was stoichiometric in the Pd(II) species. Further investigation established that the reaction was occurring via direct replacement of a β-H with a phenyl group.[160] Interestingly this type of reaction had not been observed in the presence of Pd(0) salts.

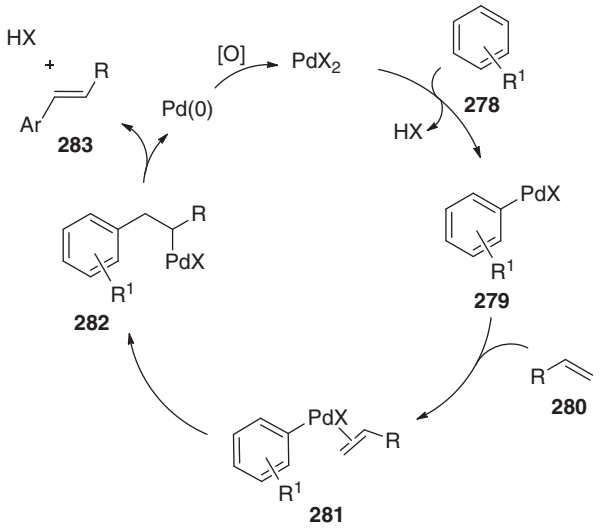
They subsequently investigated whether regeneration of the Pd(II) species would allow the reaction to proceed catalytically, through the use of an oxidant. This reaction was made catalytic in Pd(II) by employing oxidants such as AgOAc or $Cu(OAc)_2$ (Scheme 21).[161]

The usefulness of this C–H activation however could potentially be curtailed by regioselectivity issues if more than one C–H is available for substitution. Following the initial discovery of the reaction, a series of substituted aromatic compounds were screened. It was found that electron-donating groups were *ortho*-/*para*-directing and electron-withdrawing groups were *meta*-directing.[162]

The substituents on the olefin have a significant influence on reactivity.[163] Early investigations suggested that electron-withdrawing groups on the olefin enhanced the substitution compared with electron-donating groups.

4.14.7.3 Choice of Oxidant

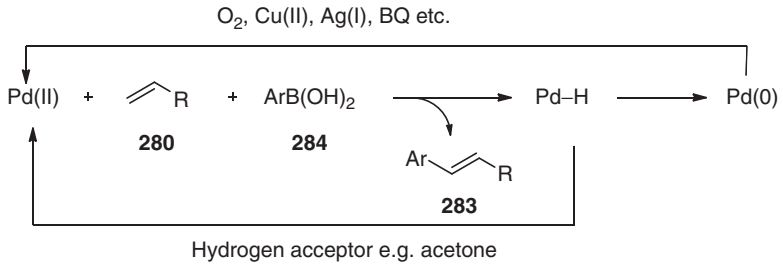
The choice of oxidant used in the Fujiwara–Moritani reaction has a dramatic effect on the reaction yields. The original oxidants used, AgOAc and $Cu(OAc)_2$, were often associated with low turnover numbers. The use of benzoquinone (BQ) as an oxidant with



Scheme 21

the inexpensive *t*-butyl hydroperoxide as a cooxidant gave high turnover numbers.[164] Molecular oxygen was also found to be a suitable oxidant for the catalytic reaction.[165]

Recently Xiao developed a system which employed a hydrogen acceptor to reoxidise Pd(0) to Pd(II) (Scheme 22).[166] This was a landmark development as it expanded the scope of the reaction to include substrates which are sensitive to the oxidizing conditions previously employed in the oxidative Heck reaction. Although this is an exciting development, it so far has not been used in the Fujiwara–Moritani reaction but exclusively in the oxidative Heck reaction involving boronic acids and olefins.



Scheme 22

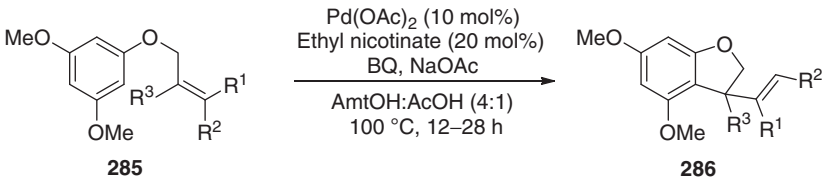
4.14.7.4 Intramolecular Fujiwara–Moritani Reaction

Stoltz performed an oxidative Fujiwara–Moritani reaction in his synthesis of functionalized benzofurans and dihydrobenzofurans.[167] However, their methodology was confined to electron-rich arenes. The reaction employed $Pd(OAc)_2$ and ethyl nicotinate as the catalyst system which generated benzofurans via an intramolecular cross-coupling reaction. Optimization led to the use of BQ as the oxidizing agent and addition of sodium acetate gave increased yields. In order to probe the reaction scope a number of substrates were subjected to the ring closure. It was found from this screen that the reaction could accommodate different substrates including tetrasubstituted olefins, to afford dihydrobenzofurans (**287–289**) in good yields (55–80%) (Table 14).

4.14.7.5 Intermolecular Fujiwara–Moritani Reaction

The Fujiwara–Moritani reaction has been extensively exploited in the functionalization of indoles which can undergo substitution at either the C2 or C3 position. It was found that the solvent/oxidant combination had profound effects on the regioselective outcome of this reaction (Table 15). Gaunt showed that performing the reaction in DMF or other polar solvents such as DMSO that C3 selectivity was observed (entries i, ii).[168] The use of 1,4-dioxane/AcOH (3:1) as the solvent mixture with *t*-BuOOBz as the oxidant resulted in preferential C2 substitution (entry iii). Interestingly, the addition of DMSO to this solvent mixture changed the preferred selectivity from C2 to C3 (entry iv).

Table 14 Oxidative Heck reaction in the synthesis of dihydrobenzofurans



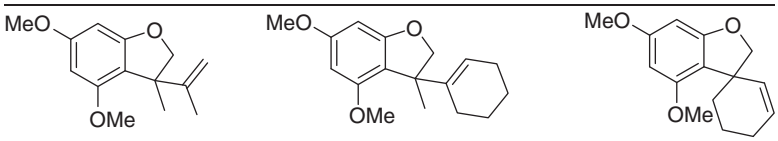
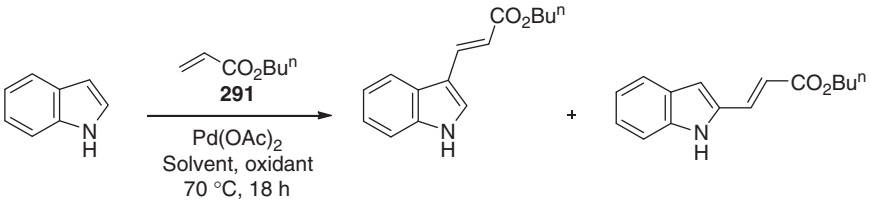


Table 15 Effects of solvents on regioselectivity



Entry	*Oxidant*	*Solvent (V:V)*	*Yield (%)*	*C3/C2*
i	$Cu(OAc)_2$	DMF	54	>95/5
ii	$Cu(OAc)_2$	DMSO	66	>95/5
iii	*t*BuOOBz	1,4-Dioxane/AcOH(3:1)	58	1/7
iv	*t*BuOOBz	1,4-Dioxane/AcOH/DMSO(3:1:0.4)	66	>95/5

Directing groups on the nitrogen atom were also found to control the regioselective outcome of the intermolecular Fujiwara–Moritani reaction (see Section 4.14.5 on chelation control). Ricci demonstrated that the presence of an *N*-benzyl group resulted in C3 substitution whereas a 2-pyridylmethyl group led to substitution at the C2 position due to coordination of Pd to the nitrogen to form a palladacycle (Figure 11).[169]

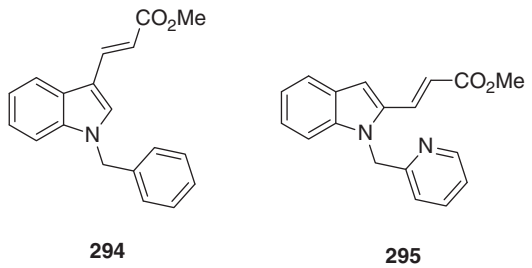
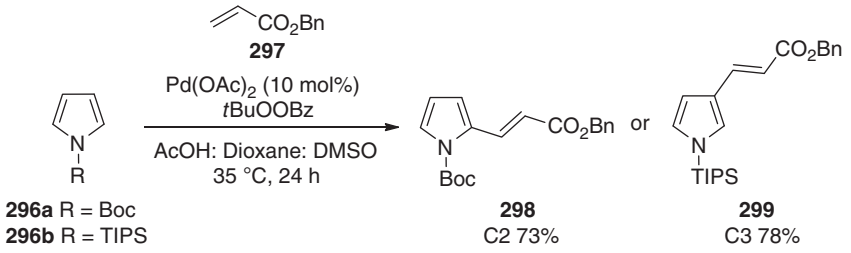


Figure 11 Regioselective outcome associated with *N* directing group.

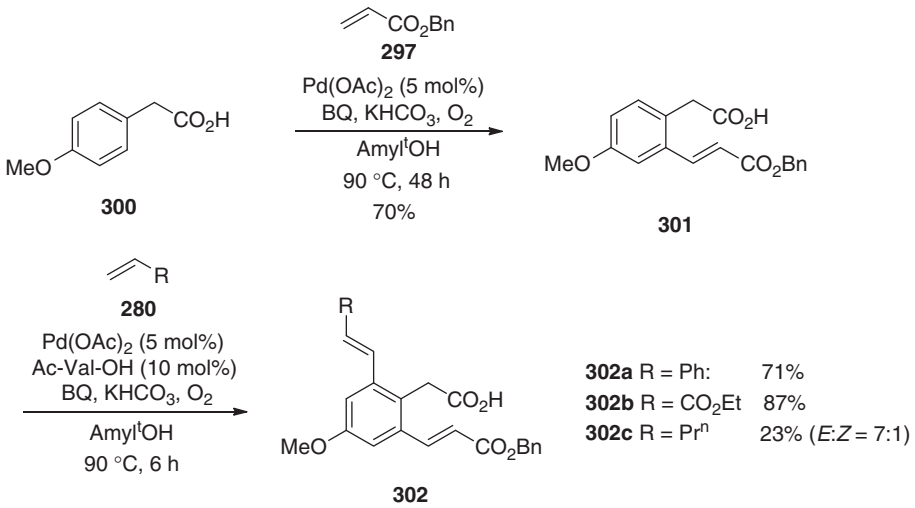
Gaunt also described the importance of directing groups on the substitution pattern of pyrroles.[170] They showed that *N*-protection with electron withdrawing-groups such as *N*-Boc, and *N*-Ac resulted in C2 selectivity, whereas use of bulky protecting groups resulted in C3 substitution, presumably due to steric interactions (equation 48).



(48)

4.14.7.6 Multisubstituted Arenes

Yu synthesized divinylbenzenes via an oxidative C–H activation protocol.[171] This methodology surpasses traditional cross-coupling methods as it does not require any manipulations of the arene to introduce suitable functionalities. They successfully synthesized unsymmetrical arenes via the sequential reaction with different olefins. Carboxylic acid directing groups were required to substitute C–H bonds in the *ortho*-position. Possible limitations of this process are disubstitution with the first alkene or the unreactivity of monosubstituted intermediates. Yu demonstrated that tuning of the Pd(II) catalyst to affect selectivity and reactivity could be achieved through the addition of ligands. It was found that the activity of the Pd (II) catalyst was enhanced by the introduction of an amino acid ligand, an improvement which led to the synthesis of unsymmetrical tetrasubstituted arenes (Scheme 23).



Scheme 23

4.14.7.7 Other Oxidative Heck Reactions

Although the Fujiwara–Moritani reaction was the first Pd(II) type oxidative Heck reaction to be observed it is not the only one. The oxidative Heck reaction between boronic acids and olefins has received a substantially greater degree of attention compared with its C–H activation counterpart. First reported by Uemura, it overcomes the regioselectivity issues associated with C–H activation.[172] The availability of a tremendous range of boronic acid substrates, primarily used for Suzuki cross-coupling, and the low toxicity associated with such compounds make them attractive components for Heck reactions.

4.14.7.7.1 Intermolecular oxidative Heck

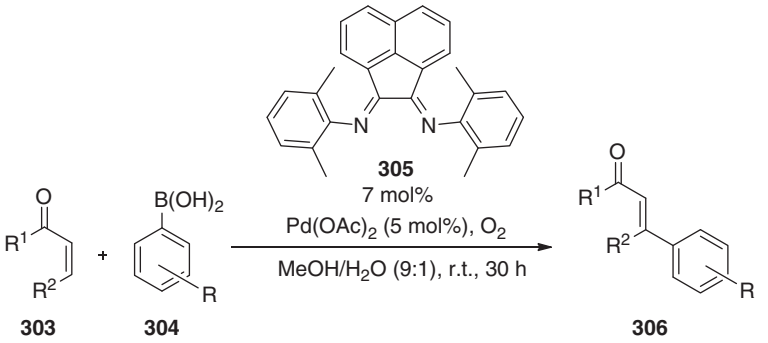
4.14.7.7.1.1 Reaction with Michael acceptors

The oxidative Heck reaction can be used to selectively form the Heck product over the conjugate addition product under mild reaction conditions on Michael acceptors.[173] It was observed that the Heck product was formed in the presence of $Pd(OAc)_2$ combined with a diimine ligand (Table 16).

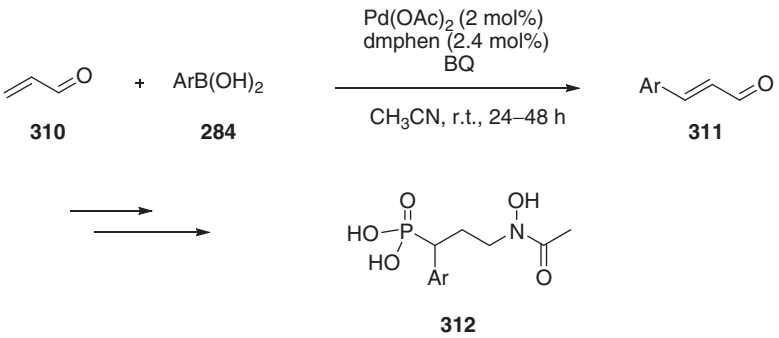
The methodology was applicable to a range of substrates. *Ortho*-, *meta*-, and *para*-substituted boronic acids were successfully coupled with the Michael acceptor, although *ortho*-substituted boronic acids gave lower yields due to steric effects.

This methodology was also applied by Larhed and coworkers toward the synthesis of *Mycobacterium tuberculosis* reductoisomerase inhibitors (**312**) for biological testing (Scheme 24).[174]

Table 16 Oxidative Heck reaction on Michael acceptors



307	308	309
81%	55%	92%



Scheme 24

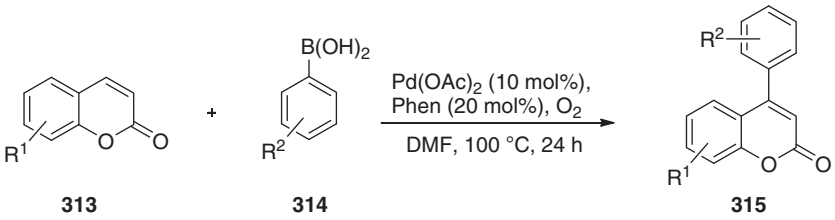
Flavones and neoflavones are desirable synthetic targets as they have numerous biological properties such as anticancer[175] and antibacterial[176] activity to name but a few. Recently the synthesis of these compounds via an oxidative Heck reaction was reported by Shafiee who used arylboronoic acids in the arylation of coumarins and chromenones (Table 17).[177]

The oxidative cross-coupling could be performed in the presence of aryl chloride bonds (entry 3) which provides a functional handle for further modification of the system. It also tolerates the presence of a phenol (entry 4) which has been shown to be essential for biological activity. Duan also reported the formation of 4-arylcoumarins using a phen-NO_2 ligand in an identical synthetic approach.[178]

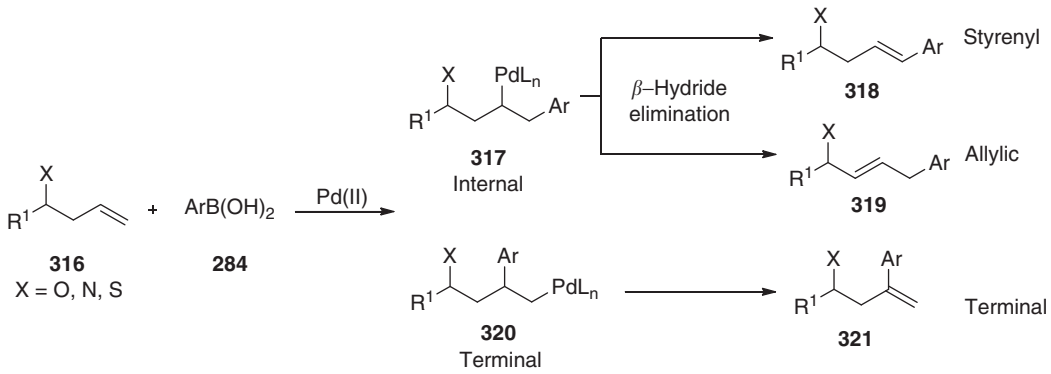
4.14.7.7.1.2 Regioselectivity issues

Although the use of a boronic acid overcomes the regioselectivity issue often associated with C–H activation, there is still the issue of whether addition to the olefin is internal or terminal. Internal addition can often result in a mixture of styrenyl and allylic products (Scheme 25).

Table 17 Synthesis of coumarins via an oxidative Heck reaction



Entry	*R^1*	*R^2*	*Yield (%)*
1	6-NO_2	H	72
2	7-OCH_2CH_3	H	74
3	7-Cl	4-CH_3	82
4	7-OH	4-CH_2CH_3	68



Scheme 25

White developed a chelation controlled, highly selective oxidative Heck reaction.[179] They demonstrated that remote olefins could react with an excellent regioselectivity through the formation of five- to seven-membered ring chelate complexes between the heteroatom X and the olefin (Table 18).

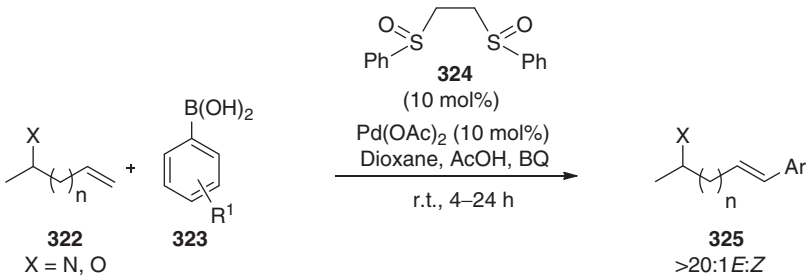
4.14.7.7.1.3 Use in the preparation of tetrasubstituted olefins

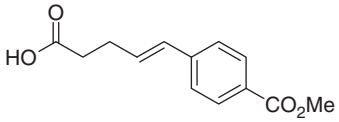
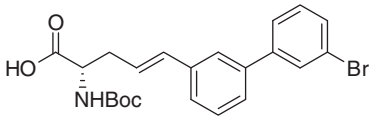
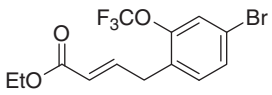
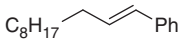
Studer recently developed methodology for the stereoselective synthesis of tetrasubstituted olefins and applied their methodology to the synthesis of *Z*-Tamoxifen (Scheme 26).[180] Starting from methyl acrylate a *trans*-alkene was synthesized through the reaction with a boronic acid under oxidative Heck conditions in the presence of TEMPO as the oxidant. A second aryl group was added by using the more reactive $Pd(OAc)_2$ as the Pd source in place of $Pd(acac)_2$. The best results for the second arylation were obtained with electron-poor boronic acids. With the trisubstituted olefin in hand, their attention was turned to the synthesis of the tetrasubstituted alkene. In order for this to work the ester was reduced to the allylic alcohol and electron-rich boronic acids were successfully coupled. The synthesis of these highly substituted olefins required the use of nitroxides as oxidants. The stereoselectivity of the reaction was highly dependent on the oxidant used.

4.14.8 Asymmetric Heck Reactions

This section provides an up-to-date survey of the literature concerning the inter and intramolecular asymmetric Heck reactions. Relevant early literature to give the foundation of these studies will be described, but an emphasis will be placed on advances reported in the past 10–15 years. Therefore, the coverage will not be exhaustive but will include only those papers, in the opinion of the authors, which satisfy the requirements of this chapter.

Table 18 Highly regioselective oxidative Heck reaction



Entry	*Product*	*Internal/Terminal*	*Styrenyl/Allylic*	*Yield (%)*
1	 **326**	>20:1	>20:1	80
2	 **327**	>20:1	>20:1	61
3	 **328**	>20:1	<1:20	60
4	 **329**	8:1	1:1	68

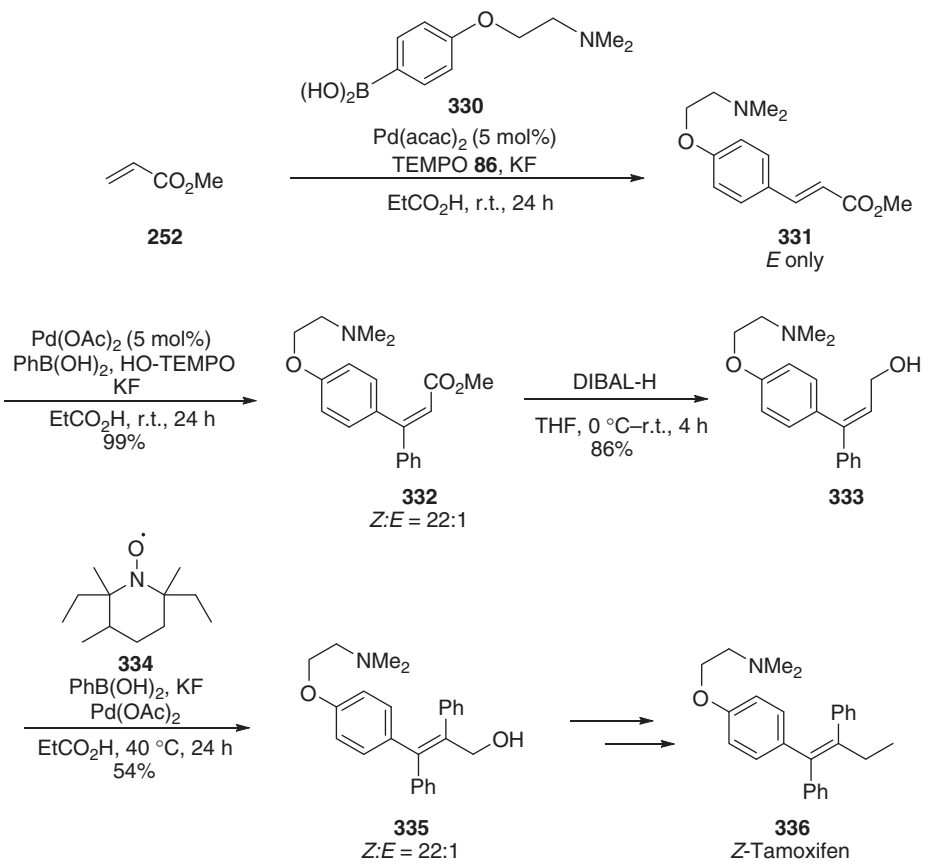
The enantioselective-determining step is the insertion of alkene into the R^1-Pd bond via either the π-neutral or the π-cationic complex, (Scheme 1, step **B**). As a rule, the cationic pathway gives rise to high levels of enantioselectivity because the ligand remains bound in a bidentate manner to the Pd complex during the insertion process whereas, in the neutral pathway, the partial dissociation of the bidentate ligand reduces the influence of the ligand and lowers the enantiomeric excess. It is worthwhile noting that important exceptions have been reported in which high levels of enantioselectivities have been observed using the neutral pathway.[10,181] The enantioselectivity is also influenced by the stereoelectronic properties of the substrates and the nature of the ligands.

4.14.8.1 The Asymmetric Intermolecular Heck Reaction

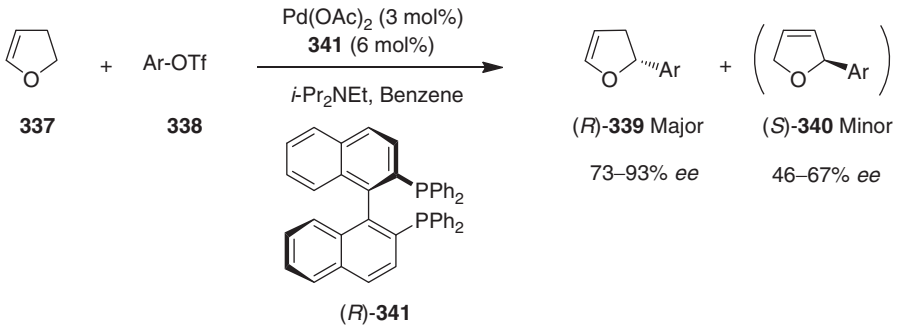
The design and application of new chiral ligands has been pivotal to reaction enhancement of the asymmetric intermolecular Heck reaction. For this and subsequent Heck and related process described herein, we classify these chiral ligands by the nature of the denticity, chirality, and donor atoms involved. In this manner, the continued development of ligand architectural design and application can be more easily monitored for each process.

4.14.8.1.1 [P,P] Ligands in the asymmetric intermolecular Heck reaction

The first example of the asymmetric intermolecular Heck reaction was reported by Hayashi and coworkers in 1991.[182] This involved the asymmetric arylation of 2,3-dihydrofuran **337** with aryl triflates **338** using the Pd/(*R*)-BINAP **341** catalytic system (equation 49). One noteworthy feature of this asymmetric reaction is that the products, **339** and **340**, are of opposite configuration, which was explained by a kinetic resolution process.[25]



Scheme 26



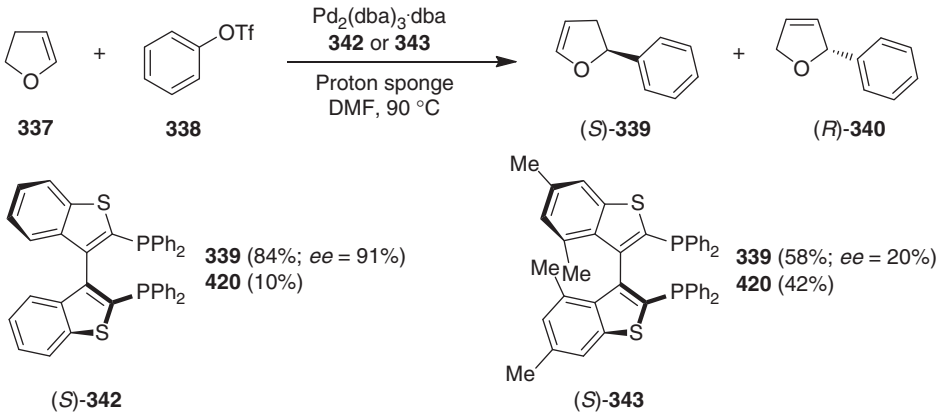
(49)

Ar = Ph, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-CH$_3$CO$_6$H$_4$, 4-NCC$_6$H$_4$, 2-naphthyl

Although BINAP **341** has been one of the most successful ligands employed in the intermolecular asymmetric Heck reaction, many other related axially chiral diphosphine ligands have also been synthesized and tested.[183] Sannicolò prepared novel thiophene-derived axially chiral diphosphine ligands **342** and **343** and applied them to the intermolecular Heck reaction of 2,3-dihydrofuran **337** using proton sponge (1,8-bis-(dimethylamino)-naphthalene) as the base (**Scheme 27**).[184]

Since the pioneering work of Hayashi, the Pd/BINAP **341** system has been extended to the synthesis of various oxygen- and nitrogen-containing heterocycles: 2-alkenyl-2,3-dihydrofuran derivatives **344**[185] and **345**,[186] 5-aryl-2,2-dialkyl-2,5-dihydrofuran **346**,[187] 2-substituted-2,3-dihydropyrroles **347** and **348**,[182b] 3-(1-naphthyl)-2,3-dihydropyrrole **349**,[188] and enol ethers **350**[189] (**Figure 12**).

Keay synthesized the novel furan-derived diphosphine ligands, TetFuBINAP **351** and BINAPFu **352**, and applied them to the asymmetric intermolecular Heck reaction of 2,3-dihydrofuran **337** and phenyl triflate **338** (**Figure 13**).[190] These ligands were found, after optimization studies, to give good-to-excellent enantioselectivities. The TetFuBINAP ligand **351**, although a less active catalyst than (*R*)-BINAP **341**, was found to give *ee*s of up to 86%. Pd complexes of BINAPFu **352** afforded high enantioselectivities



Scheme 27

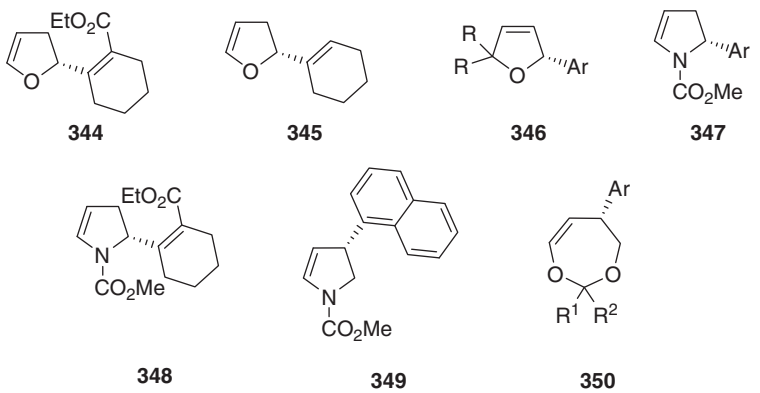


Figure 12

(>97% *ee*) although the reaction time needed to be increased to 9 days in order to get a conversion similar to that of (*R*)-BINAP **341**.

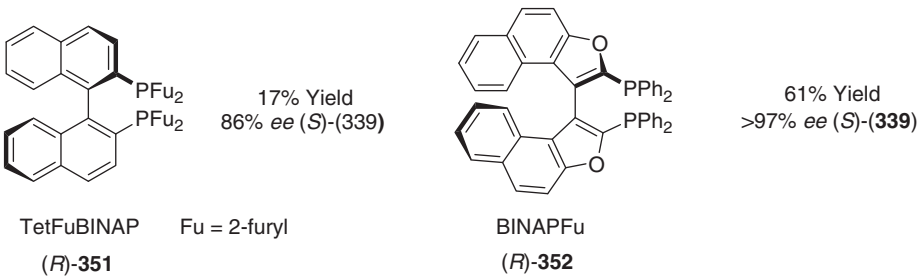


Figure 13

Keay also reported the use of two series of diphosphine ligands possessing axial chirality: 3,3′-bis(substituted)-MeO-BIPHEP **353**[191] and 3,3′-disubstituted BINAP ligands **354** (Figure 14).[192] In the reaction of 2,3-dihydrofuran **337** with phenyl triflate **338**, ligands **353e** and **354b** turned out to be optimal. In these cases, **339** was obtained quantitatively after 24 h with a very low amount of isomer **340** (**339**/**340**=99/1). Ligand **353e** gave **339** with 90% *ee* whereas **354b** afforded **339** in 73% *ee*, which were higher than that obtained with (*S*)-BINAP under the same conditions (conversion=32%, **339**/**340**=91/9, *ee*=66%).

In addition, Keay investigated the *m*-xylyl analogs in a range of 3,3′-disubstituted BINAP derivatives **355** (xylBINAP).[193] Pd complexes of ligands **355d** and (S_{ax})-**355b** gave the best results in the phenylation of 2,3-dihydrofuran with PhOTf (Scheme 28). For example, the complex derived from **355d** gave a mixture of **339** and **340** in a 99:1 ratio, with **339** produced in 83% *ee*. A similar regioisomeric ratio of 98:2 was obtained when (S_{ax})-**355b** was employed but in this case **339** was formed with an excellent *ee* of 99%.

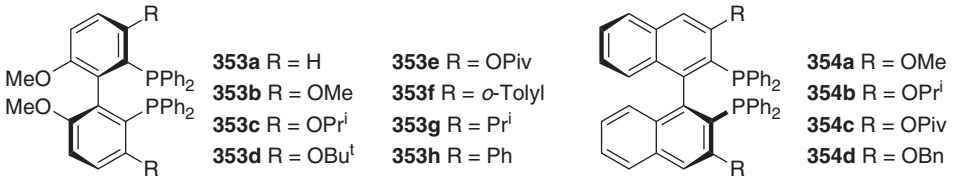
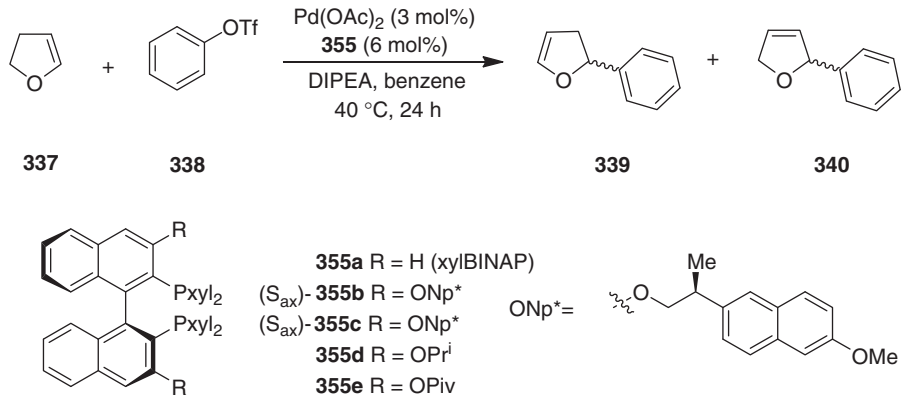
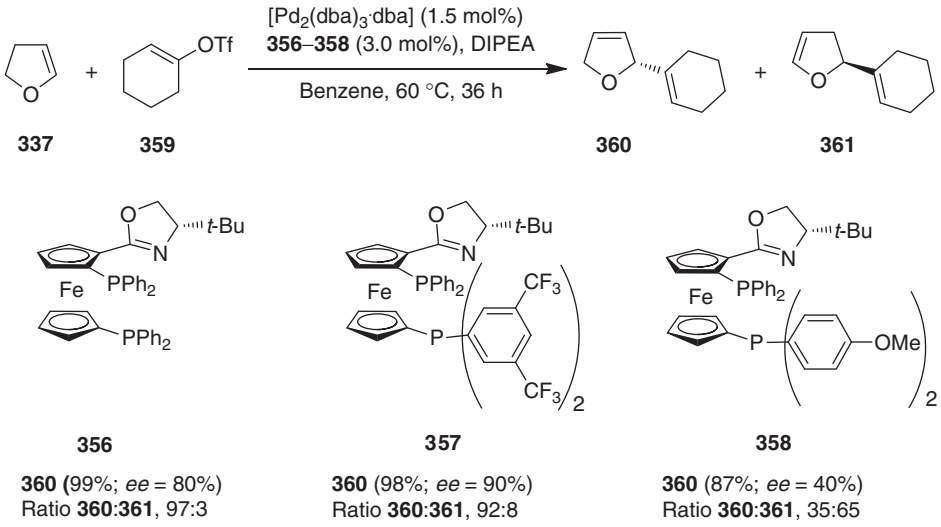


Figure 14



Scheme 28

The chiral [*P,P*] ligands **356–358**, synthesized by Hou and Dai, possess both a chiral center (oxazoline moiety) and planar chirality (ferrocene).[194] These diphosphine oxazoline ferrocene ligands were applied to the asymmetric intermolecular Heck reaction of 2,3-dihydrofuran **337** and cyclohexenyl triflate **359** (Scheme 29). With 3 mol% of Pd prepared *in situ*, the reaction was completed in 36 h affording **360** and **361** in excellent conversions in all cases. The highest enantioselectivity was observed with the 3,5-di(trifluoromethyl)phenyl-substituted phosphine ligand **357** where an *ee* of 90% was obtained. When the ligand was modified to the 4-methoxyphenyl-derived analog **358**, the *ee* dropped to 40%. Interestingly, the regioselectivity dropped from 97:3 of **360**:**361** with ligand **356** to 35:65 with ligand **358.** This dramatic change is presumably due to an electronic effect on the phosphine donor atom.[195]



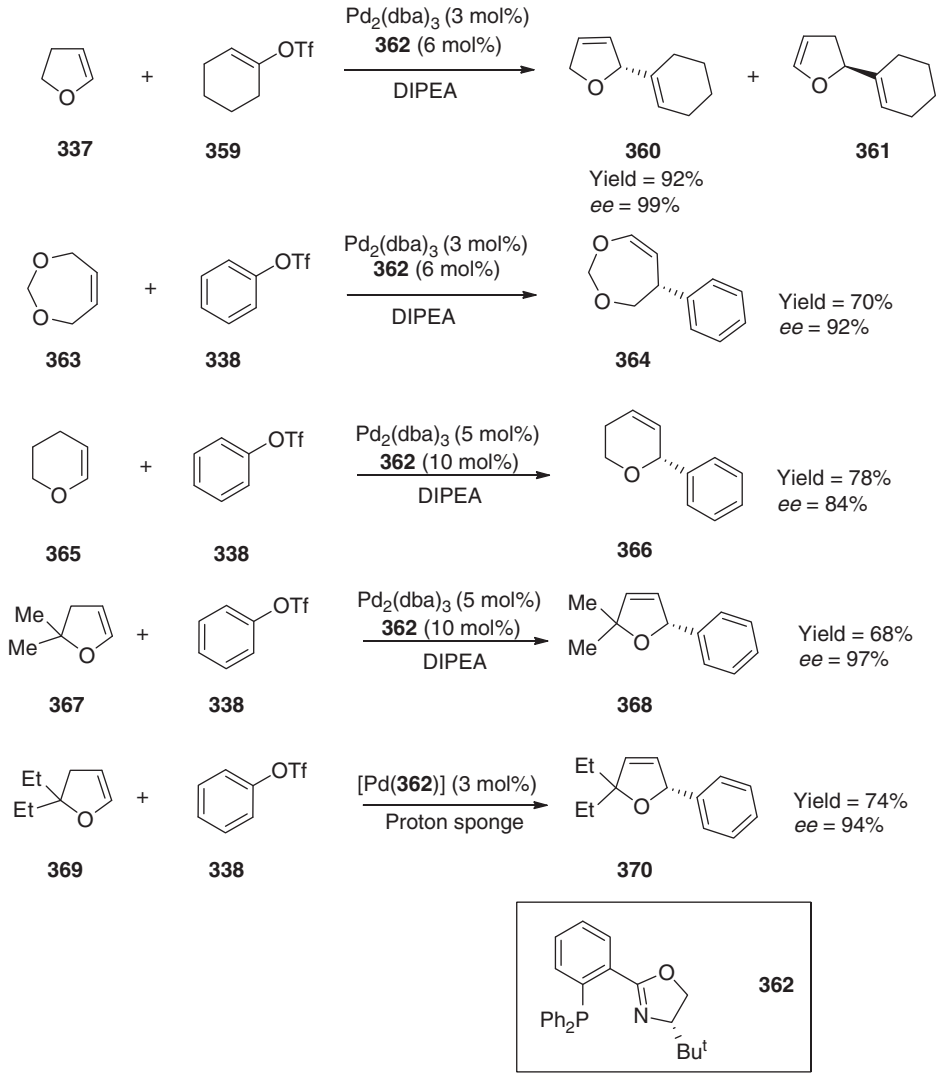
Scheme 29

4.14.8.1.2 [P,N] Ligands in the asymmetric intermolecular Heck reaction

To date, the large majority of asymmetric Heck reactions reported have utilized Pd complexes of BINAP **341** (*vide supra*). However, since their first application to the asymmetric Heck reaction, [*P,N*] ligands have proven successful and have thus received a greater

amount of attention recently.[196] Oxazoline-containing ligands have found a widespread use in asymmetric processes due to their ease of synthesis, modular nature, and applicability in a large range of metal-catalyzed transformations and organocatalyzed reactions.[197] These features combined with phosphorus-containing groups have enabled the design of modular chiral [*P,N*] ligands for the intermolecular asymmetric Heck reaction.

With this aim, the phosphinooxazoline [*P,N*] ligands PHOX have shown dramatic improvement in enantioselectivity in a number of asymmetric transformations including the intermolecular asymmetric Heck reaction.[198] As an example, when the *t*-leucinol-derived ligand **362** was applied in the cyclohexenylation of 2,3-dihydrofuran **337** using $Pd_2(dba)_3$ and DIPEA as base, the reaction proceeded in 92% yield for **360** and with 99% *ee* (Scheme 30). The most surprising result was the low amount of double-bond isomerization observed. In fact, only trace amounts of the isomerized product **361** were formed compared with BINAP, where it is the more stable, isomerized product **361** that predominates. Similar results were achieved when phenyl, 1-naphthyl, and 1-cyclopentyl triflate were used as reagents.

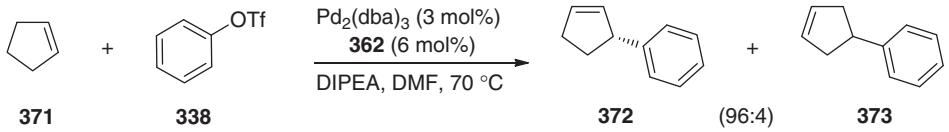


Scheme 30

The intermolecular Heck reaction of 4,7-dihydro-1,3-dioxepin **363** with phenyl triflate **338** to provide **364** also proceeded with good yield and high enantioselectivity (70%, 92% *ee*) compared with the corresponding Pd(BINAP) complex (84%, 72% *ee*). Dihydropyran **365** proved to be less reactive than 2,3-dihydrofuran **337** but, at higher temperatures and catalyst loading, **366** was produced in high yield and enantioselectivity (78%, 84% *ee*). As with BINAP **341**, Guiry tested ligand **362** in the phenylation and cyclohexenylation of 2,2-dimethyl-2,3-dihydrofuran **367** and 2,2-diethyl-2,3-dihydrofuran **369**, forming **368** and **370**, respectively, in yields of up to 100% and *ee*s of up to 97% (Scheme 30).[187]

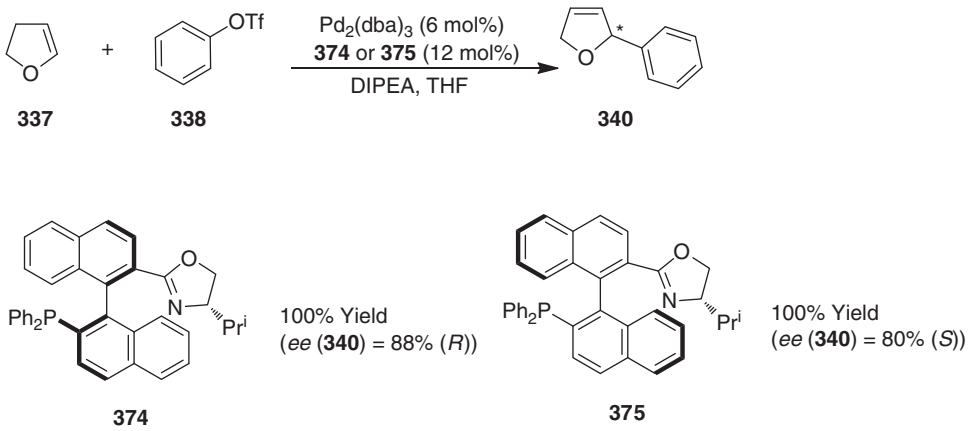
The low amounts of double-bond isomerization observed using these ligands made it possible to consider using substrates such as cyclopentene **371** which are converted to a mixture of isomers with Pd complexes of BINAP **341** as catalysts.

The phenylation of cyclopentene **371** proceeded with high regioselectivity for the unisomerized product **372** in 85% yield and 91% *ee* whereas the use of BINAP **341** gave a mixture of regioisomers (equation 50). Moreover, Pd-catalyzed asymmetric reactions have been performed using [*P,N*] ligand **362** under MW heating.[199] Under these conditions, the reaction time for the coupling of **337** with phenyl triflate **338** is reduced to 4 h (compared with 4 days under thermal conditions) giving **340** in good yield (85%) and high *ee* of 88% (under thermal conditions, 97% *ee* was obtained). This work has been extended to asymmetric arylations of **371** as well as use of BINAP **341** as ligand.



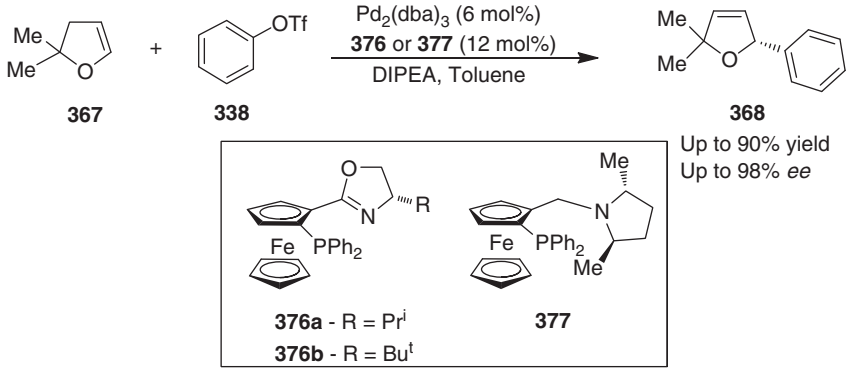
(50)

Given the success of the PHOX ligands, Hayashi and Ikeda independently synthesized (S,S_P)- and (S,R_P)-2-[4-(isopropyl)oxazole-2-yl]-2′-diphenylphosphino-1,1′-binapthyl ligands **374** and **375**.[200,201] Hayashi tested these ligands in the intermolecular Heck reaction of phenyl triflate **338** and 2,3-dihydrofuran **337**. Complete conversions with *ee*s up to 88% were achieved whereas none of the double-bond isomer **339** was observed (**Scheme 31**). In addition the catalyst derived from ligand **375** proved more reactive than that derived from ligand **374**, albeit with slightly lower enantioselectivity. Interestingly the two ligands **374** and **375** induced opposite configurations in the product leading to the conclusion that the axial chirality is the more influential element in the intermolecular Heck reaction.[202]



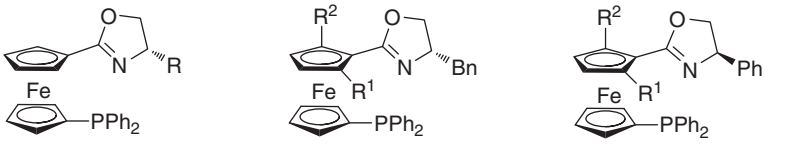
Scheme 31

Guiry reported the application of ferrocene-based [*P,N*] ligands **376** and **377** to the Heck reaction of 2,2-dialkyl-2,3-dihydrofurans with phenyl and cyclohexenyl triflates.[203] The reaction proceeded in good yields and excellent enantioselectivities (up to 90% yield and 98% *ee*) when Pd complexes of ligand **376b** were employed (equation 51). The related [*P*,N] ligand **377** gave poor levels of enantioselectivity (up to 24% *ee*).



(51)

The major drawbacks with many intermolecular Heck reactions are the long reaction times and high catalyst loadings required to get substantial conversions. Hou overcame this somewhat when they applied 1,1′-disubstituted and 1,1′,2′-substituted-[*P*,*N*]-ferrocene ligands (**378–380**) to the intermolecular Heck reaction (Figure 15).[194] These ligands were tested in the phenylation of 2,3-dihydrofuran **337**. The reactions were carried out at 60 °C for 8 h with 6 mol% of ligand. A benzyl or phenyl substituent on the oxazoline, ligand **378b** and **378d**, respectively, proved to be the most effective giving rise to 80% and 79% conversions, respectively. With this in mind, planar chiral ligands **379** and **380** were prepared. A dramatic change in the enantioselectivity of the reaction was observed with ligand **379a** containing a trimethylsilyl group. The enantioselectivity changed from 77% (*R*) to 84% (*S*). They also tested ligand **379b**, which has opposite planar chirality, and this reversed the enantioselectivity giving 89% (*R*). The same effect in enantioselectivity was observed with ligands **380**, leading to the conclusion that planar chirality plays the dominant role in the enantioselectivity of the intermolecular Heck reaction. These planar chiral ligands allowed moderate reaction conditions and high enantioselectivity but they also provided access to either configuration of product simply by changing the planar chirality in the ligand.



378a R = Pr^i
378b R = Bn
378c R = Bu^t
378d R = Ph

379a R^1 = TMS; R^2 = H
379b R^1 = H; R^2 = Me
379c R^1 = H; R^2 = TMS

380a R^1 = H; R^2 = TMS
380b R^1 = Me; R^2 = H

Figure 15

The group of Gilbertson reported the class of phosphine-oxazoline ligands **381** and **382** (Figure 16), bearing a chiral phosphanobornadienyl and an oxazoline and their application to the cyclohexenylation of 2,3-dihydrofuran **337**.[204] They observed that the larger the aryl group, the faster the reaction proceeded. For example, the Pd complex of **381d** catalyzed the formation of (*R*)-**360** from the reaction of cyclohexenyl triflate **359** with 2,3-dihydrofuran **337** to completion in just 20 h at room temperature whereas the complex of **381a** required 120 h for complete reaction. However, although increasing the size of the substituent increased the reaction rate, it had the opposite effect on the enantioselectivity. The complex of **381d** gave only 56% *ee* whereas the complex of **381a** gave 76% *ee*. As was previously noted in oxazoline-containing ligands, increasing the sterics on the oxazoline unit led to an increase in enantioselectivity. Ultimately (*R*)-**340** was obtained with an *ee* of 93% was achieved using the Pd complex of ligand **381b**.

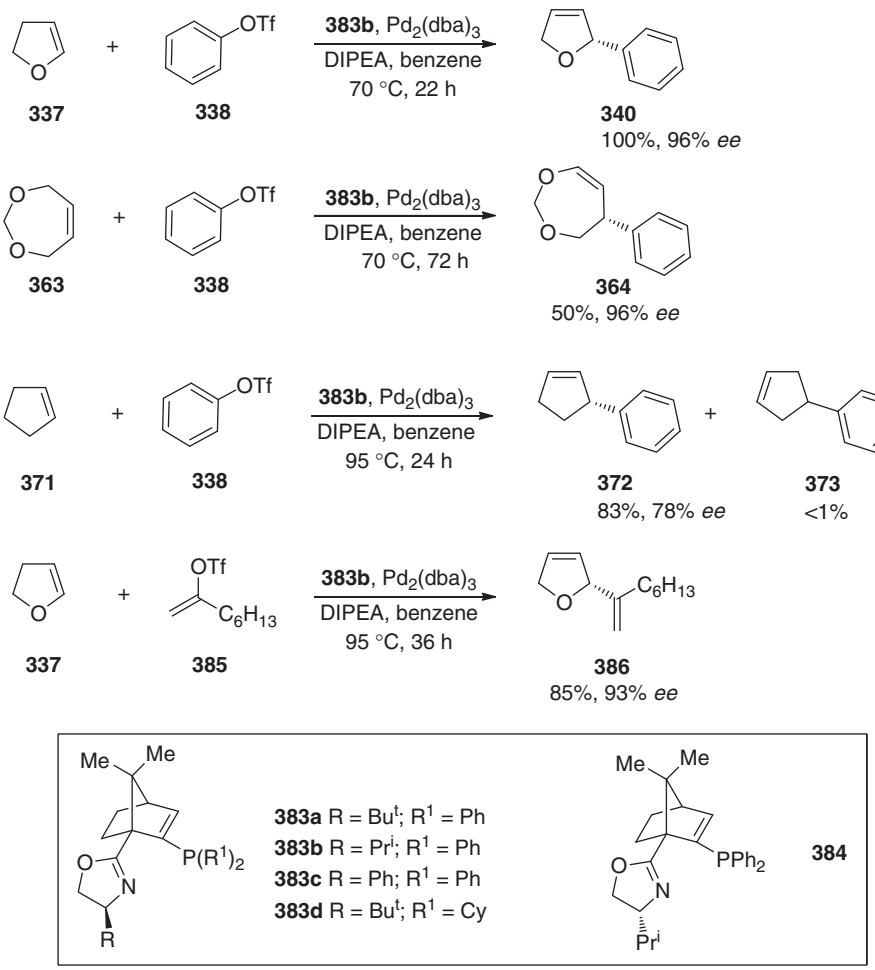
381a Ar = phenyl; R = Pr^i
381b Ar = phenyl; R = Bu^t
381c Ar = phenanthryl; R = Pr^i
381d Ar = anthracyl; R = Pr^i

382a Ar = phenyl; R = Pr^i
382b Ar = phenyl; R = Bu^t
382c Ar = phenanthryl; R = Pr^i
382d Ar = anthracyl; R = Pr^i

Figure 16

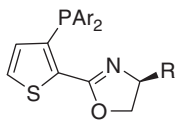
Gilbertson also reported the related phosphine-oxazolines **383** and **384** with a norbornyl backbone.[205] Preliminary results showed that ligand **383a**, bearing the *t*-Bu substituent on the oxazoline, provided the best results in the reaction of cyclohexenyl triflate **359** with 2,3-dihydrofuran **337** giving complete conversion with an *ee* of 94% after 22 h. Ligands with other substituents on the oxazoline were less reactive and afforded lower *ee*s. Also, as expected changing the stereochemistry on the oxazoline (ligand **384**) resulted in the opposite configuration of product. As before this shows that the stereochemistry is determined by the substituent on the oxazoline as opposed to the norbornyl ring. Using these ligands different coupling partners (**337**, **363**, and **371**) were tested achieving excellent *ee*s in many cases (Scheme 32).

Guiry reported the application of heterocyclic analogs of the PHOX ligands **362**, HetPHOX ligands **387** and **388**, to the phenylation and cyclohexenylation of 2,3-dihydrofuran **337** (Figure 17).[206] The ligands proved successful in both test reactions providing *ee*s and

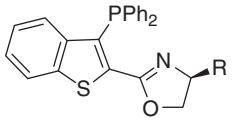


Scheme 32

conversions greater than 90% in many cases. Ligand **387e** provided the best results for phenylation (conversion = 83%, *ee* = 96%), cyclohexenylation (conversion = 99%, *ee* = 95%), and naphthylation (conversion = 99%, *ee* = 94%) reactions. These results were consistent with the PHOX ligands where it was found that the *t*-leucine-derived ligand was the most reactive and selective.



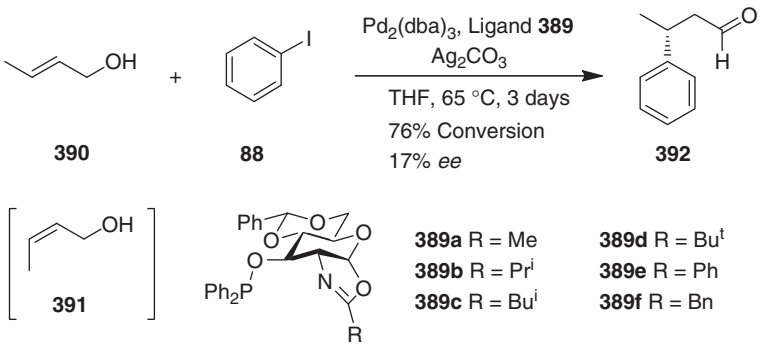
387a Ar = Ph; R = Pr^i
387b Ar = Ph; R = Bu^t
387c Ar = Ph; R = Ph
387d Ar = *o*-Tol; R = Pr^i
387e Ar = *o*-Tol; R = Bu^t
387f Ar = *o*-Tol; R = Ph
387g Ar = *p*-F-C$_6$H$_4$; R = Pr^i
387h Ar = *p*-F-C$_6$H$_4$; R = Bu^t



388a R = Pr^i
388b R = Bu^t
388c R = Ph

Figure 17

Ohe and Uemura developed the phosphinite oxazoline ligands **389**, derived from D-glucosamine.[207] They applied these ligands to the Heck reaction of phenyl triflate **338** with 2,3-dihydrofuran **337**. Ligand **389f**, bearing a benzyl substituent on the oxazoline, provided the best results for this transformation giving complete conversion with 96% *ee* after 1 day. Furthermore, these ligands were tested in the phenylation of (*E*)- and (*Z*)-crotyl alcohols **390** and **391** (Scheme 33). This was the first reported asymmetric Heck reaction of an acyclic alkene. A Heck reaction using phenyl triflate **338** did not give any product after 3 days, whereas when phenyl iodide **88** was used the reaction proceeded to afford **392** with good conversions (up to 76%) albeit with low enantiomeric excess (up to 17%).



Scheme 33

Diéguez and Pàmies synthesized similar phosphite oxazoline ligands **393** derived from D-glucosamine (**Figure 18**).[208] They applied these ligands to many Heck transformations affording in all cases the desired Heck products with high levels of enantioselectivities. One of the major drawbacks with [*P,N*] ligands is the long reaction times required to ensure full conversion. In order to decrease reaction time, MW-assisted asymmetric Heck reactions have also been carried out using ligand **393**.[208b] In the reaction of **337** with phenyl triflate **338**, the Pd complex of ligand **393** (R = Ph, $R^1 = SiMe_3$, and $R^2 = H$) gave total conversion to compound **340** with excellent regio- and enantioselectivities (**340**:**339**, 98:2 and *ee* (**340**) = 99%) after only 10 min of reaction under MW heating (70 °C). Encouraged by these results, MW-assisted reactions using **393** have been extended to other combinations of substrates, giving in all cases the desired compounds with excellent regio- and enantioselectivities.

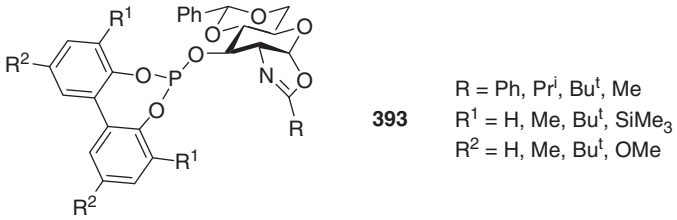
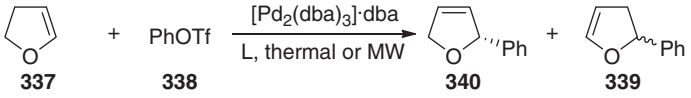


Figure 18

The scope of phosphite-oxazoline ligands was subsequently expanded by Diéguez and Pàmies with the synthesis and application of a modular library of ligands to a broad range of triflates and substrates. The effect of modifying several ligand parameters was also probed.[209] A range of sterically and electronically varied triflate sources were screened for the arylation of 2,3-dihydrofuran, with generally excellent conversions (up to 100%), regioselectivities (up to >99:1 **339**:**340**), and enantioselectivities (up to 99%). The best results were obtained with PhOTf **338** (**Scheme 34**), with excellent results also obtained with 1-naphthyl, *p*-tolyl, *p*-nitrophenyl, and cyclohexenyl triflates. The ligands were applied to the arylation of several more challenging substrates, with ligands **394**, **395,** and **396** in particular providing consistently impressive results. The decrease in reaction time provided by MW irradiation when using P–N ligands is well established, and here provided a reduction in reaction time from 1 to 3 days to 10 min to 6 h, which is a significant practical advance to the field.[199]

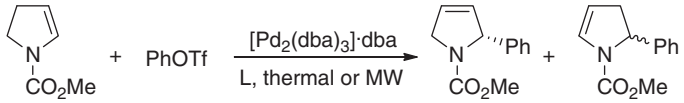
Phosphine-thiazole ligands have also benefited from application to the MW-accelerated asymmetric intermolecular Heck reaction, as reported by Andersson (**Scheme 35**).[210] Using ligand (*S*)-**406**, the reaction of *p*-tolyl triflate and 2,3-dihydrofuran gave 50% conversion with 97% *ee* of **400** and regioselectivity of (98/2 **400**:**401**). Under MW irradiation, complete conversion of starting material was obtained after 1 h. No impact on the enantio- or regioselectivity of the reaction was observed. Additional triflates were screened under identical conditions, with full conversion and excellent enantioselectivities for all aromatic triflates. Using cyclohexenyl triflate, an extended reaction time of 1.5 h was required for complete conversion, and the product was formed in 68% *ee*. Ligand (*S*)-**407**, which contained bulkier *o*-tolyl substituents on the phosphine moiety, was the most effective for reactions employing CyOTf giving 86% *ee* and regioselectivity of (98/2 **360**:**361**).

Very recently, Andersson, Pàmies, and Diéguez have reported the synthesis of a new class of [*P,N*] ligands; phosphite-oxazole/imidazole ligands of type **408** and **409** (**Figure 19**).[211] They are more robust than phosphine and phosphinite ligands, demonstrating a higher tolerance to air and oxidizing agents. A variety of phosphite-oxazole and phosphite-imidazole ligands were applied to the asymmetric intermolecular Heck reaction, using 2,3-dihydrofuran **337** as a substrate, with varying success. On conventional heating, the phosphite-imidazole ligands generally gave poor conversions with a range of triflates (up to 24% with a regioselectivity of 85:15 using **409**) and moderate–to-good enantioselectivity (up to 75% *ee* with **409**). MW heating with the same ligand increased the conversion to 69% (89:11 regioselectivity), but had little effect on the enantioselectivity. The phosphite-oxazole ligands proved more successful. Using *p*-nitro-phenyl triflate the Pd complex of **408** induced almost



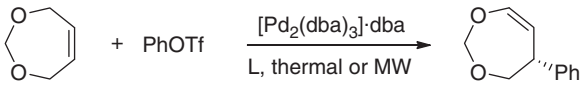
337 **338** **340** **339**

Thermal: L = **394**, 99% conversion, >99:1 (**340**:**339**), >99% *ee* (*R*)-**340**
MW: L = **396**, 100% conversion, 99:1 (**340**:**339**) 99% *ee* (*R*)-**340**



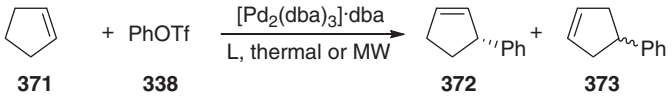
397 **338** **398** **399**

Thermal: L = **396**, 99% conversion, >99:1 (**398**:**399**), >99% *ee* (*R*)-**398**
MW: L = **394**, 90% conversion, >99:1 (**398**:**399**), 99% *ee* (*R*)-**398**



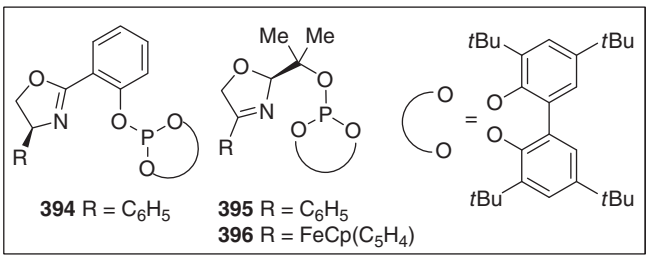
363 **338** **364**

Thermal: L = **396**, 99% conversion, 98% *ee* (*R*)-**364**
MW: L = **394**,100% conversion, 99% *ee* (*R*)-**364**



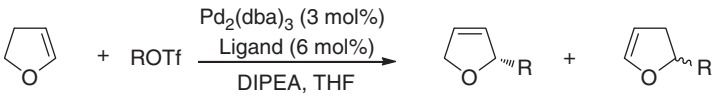
371 **338** **372** **373**

Thermal: L = **396**,100% conversion, 94:6 (**372**:**373**), 99% *ee* (*R*)-**372**
MW: L = **396**, 99% conversion, 98:2 (**372**:**373**), 99% *ee* (*R*)-**372**



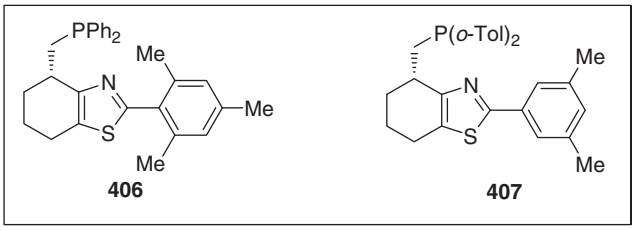
394 R = C_6H_5 **395** R = C_6H_5
396 R = $FeCp(C_5H_4)$

Scheme 34



337

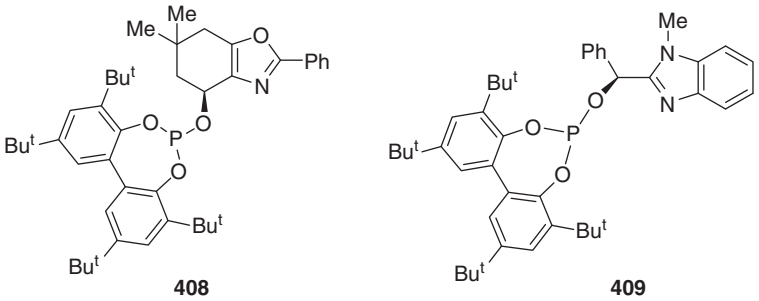
R = Ph	*ee* = 96%	**340**	**339**
R = *p*-Tol	*ee* = 97%	**400**	**401**
R = *p*-Anisole	*ee* = 94%	**402**	**403**
R = 1-naphthyl	*ee* = 98%	**404**	**405**
R = 1,2-cyclohexenyl	*ee* = 68%	**360**	**361**



406 **407**

Scheme 35

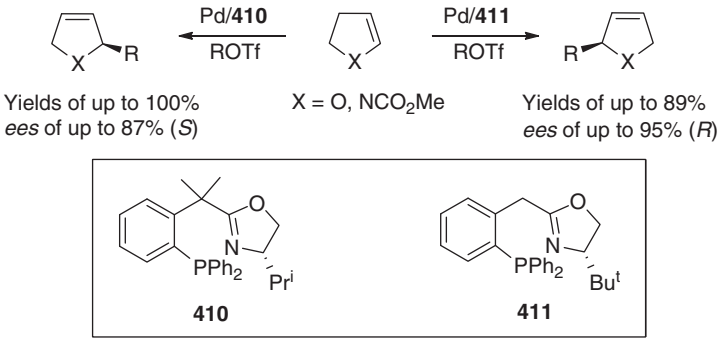
quantitative conversion, regio- and enantioselectivity. Using the same ligand Pd complex, MW heating increased the conversion of the phenylation of 2,3-dihydrofuran from 77% to 99% with a reduction in reaction time to 30 min from 24 h. Minimal effects on the regio- and enantioselectivity were observed. A range of other triflates were shown to benefited from MW irradiation.



408 **409**

Figure 19

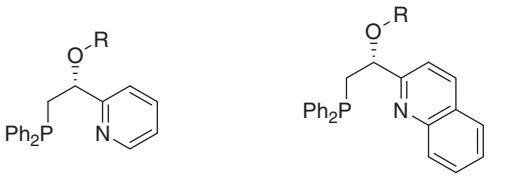
Hou prepared phosphino-oxazoline ligands **410** and **411** where the oxazoline substituent is at the benzylic position (Scheme 36).[212] The difference between these ligands and the PHOX ligands is that the chelate formed with Pd is now seven-membered. In the reaction of aryl triflate with 2,3-dihydrofuran **337** or *N*-carbomethoxy-2,3-dihydropyrrole **397**, a dramatic switch in enantioselectivity is realized using either **410** or **411** as the ligand. The Heck products of (*R*)-configuration were obtained using **411** whereas ligand **410**, with methyl substituents at the benzylic position, afforded (*S*)-configured heterocycles. DFT calculations and X-ray analysis have been carried out to explain the influence of the benzylic substitution on the enantioselectivities.



410 **411**

Scheme 36

Pfaltz developed [*P,N*] ligands **412** and **413** derived from pyridine and quinoline (Figure 20).[213] They reasoned that since oxazoline and pyridine ligands have different electronic effects, they would induce different patterns of reactivity and selectivity in the asymmetric Heck reaction. In the reaction of phenyl triflate **338** with 2,3-dihydrofuran **337**, ligand **413b** afforded the best result with complete conversion after 2 days at 50 °C with an excellent enantiomeric excess of 97%.



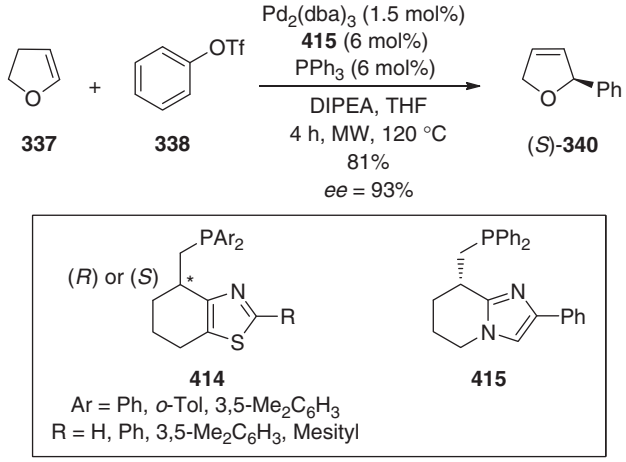
412a R = Si(Bu^t)Me$_2$
412b R = Si(Pr^i)$_3$
412c R = Si(Bu^t)Ph$_2$

413a R = Si(Bu^t)Me$_2$
413b R = Si(Pr^i)$_3$
413c R = Si(Bu^t)Ph$_2$

Figure 20

In 2007, Andersson reported the synthesis of the novel thiazole-based [*P,N*] ligands **414** and their application in the cross-coupling reaction of 2,3-dihydrofuran **337** and phenyl triflate **338** under MW heating.[210] Under these conditions, ligand (*S*)-**414** (Ar = Ph and R = mesityl) gave the best results both in terms of conversion (98% after 1 h of reaction at 120 °C) and enantiomeric

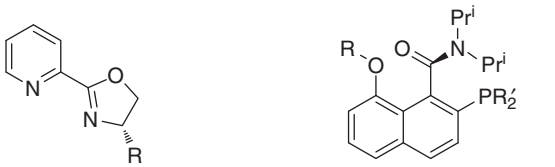
excess (96% for (*S*)-**340** without any trace of **339**). The use of such ligands have been extended to other triflate derivatives with (*S*)-**414** (Ar = Ph and R = mesityl) giving rise to excellent conversions and *ee*s in all cases in 1–1.5 h reaction times. Following this work, they applied the related imidazole-containing ligand **415** in order to study the influence of the heterocyclic ring on the asymmetric Heck reaction (equation 52).[214] By using DFT calculations and experimental studies, they showed that imidazole ligand **415** binds more strongly to Pd than the thiazole ligand **414** (Ar = Ph, R = Ph). Consequently, ligand **415** was applied to the reaction of **337** with phenyl triflate **338** under MW heating (4 h, 120 °C) with PPh_3 as an additive to give **340** in excellent yield and *ee*. In this reaction, PPh_3 acts as a Pd(0)-stabilizing and nonparticipating agent to ensure maximum conversion without altering the enantioselectivity. This has been also rationalized by computational studies.



(52)

4.14.8.1.3 Other ligand classes in the asymmetric intermolecular Heck reaction

Although not commonly used in the asymmetric Heck reaction, [*N*,*N*] donor ligands have proved successful in many asymmetric transformations. Jones and coworkers applied the 'PyOX' (pyridyloxazoline) ligands **416** (Figure 21), developed by Bolm, to the intermolecular asymmetric Heck reactions of iodobenzene and phenyl triflate **338** with 2,3-dihydrofuran **337**.[215] Pd complexes of these ligands were not as reactive or as selective in this transformation as many [*P*,*N*] ligands. Indeed using iodobenzene as substrate, they observed conversions of less than 25% along with no enantioselectivity. Using phenyl triflate **338**, again low conversions (<30%) were observed albeit with some moderate enantioselectivity (up to 60% *ee*). Dai and coworkers reported the only example of [*P*,*O*] ligands applied to the asymmetric Heck reaction (Figure 21).[216] The atropoisomeric amide-derived ligands **417** were applied to the reaction of phenyl triflate **338** and 2,3-dihydrofuran **337**. In all cases conversions were low (<30%) although moderate enantioselectivity was observed (52% *ee*, ligand **417a**).



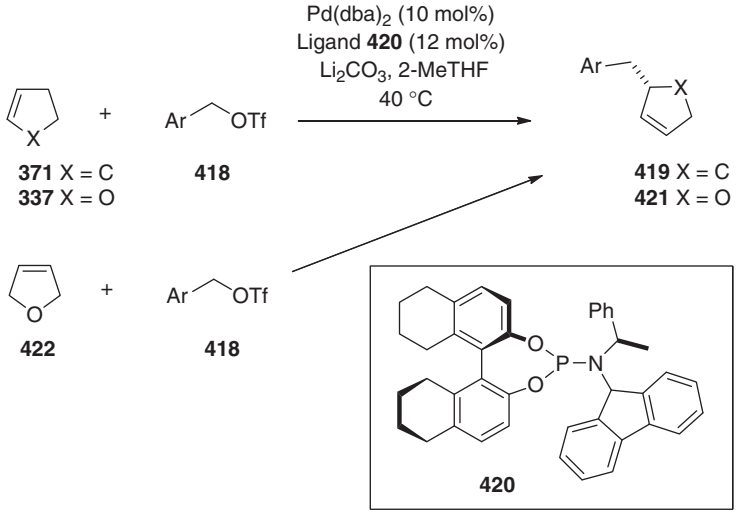
416a R = Pr^i
416b R = Bu^i
416c R = Bu^s
416d R = Bn

417a R = Me; R′ = Ph
417b R = Bn; R′ = Ph
417c R = Me; R′ = Bu^t

Figure 21

In a recent important study by Zhou the reaction between cyclopentene **371** and benzyl triflate **418** was found to afford the corresponding benzylated products **419** with high levels of enantioselectivity and little double-bond migration (Scheme 37).[217] Key to the success of this reaction was the use of phosphoramidites as chiral ligands, with ligand **420** being optimal. Both electron-donating and electron-withdrawing groups can be present on the aryl ring and the levels of enantioselectivity are decreased somewhat with the presence of *ortho*-substituents. Cyclohexene was found not to react, whereas cycloheptene gave enantioselectivities up to 60%. The leaving group on the electrophilic species was critical as only triflates were successful substrates whereas other leaving groups such as Br, Cl, OTs, OMs, OCO_2Et, OBz, and even OAc gave <5% conversion. They extended this study to include 2,3-dihydrofuran **337** as substrate and obtained **421** with very high levels of regioselectivity (from 10:1 up to 67:1) and enantioselectivities (between 89% and 97% *ee*). In addition, they found that the Pd/ligand **420** catalyst system was tolerant to

sensitive functional groups such as aldehyde and nitro groups and that the electron-donating and electron-withdrawing substituents can be present. Some heteroaryl derivatives of thiophene and furan worked well. 2,5-Dihydrofuran **422** was considered too electron-deficient a substrate for intermolecular Heck reactions. Zhou et al. applied the Pd complex of **420** to the reaction of 2,5-dihydrofuran with a series of benzyl triflates and, rather surprisingly, obtained the corresponding 2-benzyl-2,5-dihydrofurans **421 as** the major products. They obtained very high levels regioselectivity (from 17:1 up to 60:1) and enantioselectivities (between 92% and 93% *ee*).

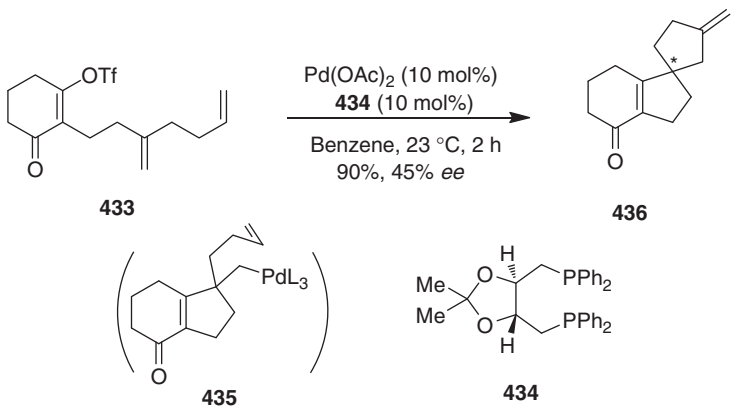


Scheme 37

Many researchers have used a wide range of ligands and ligand types, Pd(0) precursors, bases, and solvents in order to optimize the specific transformations studied. Taking 2,3-dihydrofuran as an example, we feel it would be beneficial to summarize what, in the opinion of the authors, are the best systems which afford optimal yields, regioselectivity and in particular enantioselectivity. The [*P,N*] ligand class appears to be superior for the intermolecular asymmetric Heck reaction, with the ubiquitous *t*-Bu PHOX ligand **362** consistently providing excellent *ee*s for many transformations, although in moderate-to-high yields. More recently, the phosphite-oxazoline ligands **394–396** developed by Diéguez and Pàmies have provided superior yield, regio- and enantioselectivity for all model substrates commonly employed. In addition, their suitability for MW-accelerated reactions places makes them the most attractive choice.

4.14.8.2 The Asymmetric Intramolecular Heck Reaction

The asymmetric intramolecular Heck reaction was reported initially in 1989 when Overman and Shibasaki independently described enantioselective cyclizations.[218] Two strategies have been developed in order to maintain the sp^3 center initially formed after migratory insertion. One means of maintaining the stereogenic center relies on the fact that the resultant intermediate does not contain a β-hydrogen. The Pd intermediate thus formed may then undergo a subsequent reaction in a tandem Heck process. Overman's seminal report described a polyene cyclization of a trienyl triflate **433** using $Pd(OAc)_2$ and (–)-DIOP **434**, which proceeded via such a tandem Heck process yielding the tricycle **436** in 90% yield and 45% *ee* via the intermediate **435** (equation 53). Alternatively, if cyclic alkenes are used as substrates the hydrogen at the newly formed sp^3 center must always be *anti* to Pd. As the intermediate is cyclic, bond rotation is not possible and therefore β-hydride elimination must occur away from the stereogenic center.

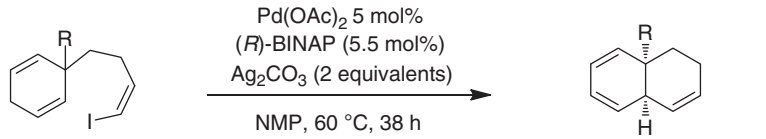


(53)

This approach was used for the enantioselective synthesis of a range of cyclic structures, including decalins, hydrindans, and diquinanes. In addition, the synthesis of quaternary stereogenic centers has been developed using the intramolecular asymmetric Heck reaction and important advances will be detailed in the following sections.

4.14.8.2.1 Asymmetric synthesis of decalins

The group of Shibasaki synthesized the optically active (*Z*)-decalin derivatives **438**, from the corresponding alkenyl iodides **437**, employing this desymmetrization strategy (Scheme 38).[218b] After screening a number of bisphosphine ligands, BINAP **341** was found to be the most effective. The reaction conditions employed, although somewhat similar to nonenantioselective versions, differed crucially in the choice of ligand and solvent. Very low enantioselectivities were obtained using solvents such as THF or DMSO (commonly used Heck solvents), with the preferred solvent being *N*-methyl-2-pyrrolidinone (NMP).

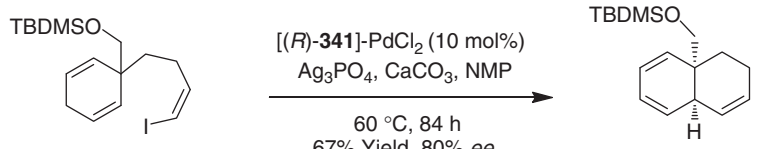


437a R = CO_2Me
437b R = $CH_2OTBDMS$
437c R = CH_2OAc

438a (74%; 46% *ee*)
438b (70%; 44% *ee*)
438c (66%; 36% *ee*)

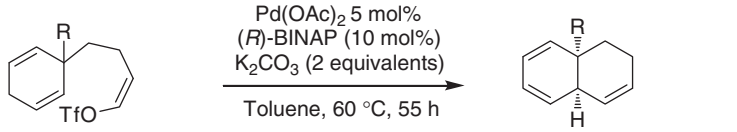
Scheme 38

Only moderate *ee*s were observed (33–46%) in this initial report. BINAP **341** proved to be the ligand of choice and a subsequent report by the same group investigated the effect of added silver salt.[219] It was ascertained that using similar reaction conditions, but also adding 2 M equivalents of Ag_3PO_4 as halide scavenger, led to an increase in enantioselectivity to 80% (equation 54). The silver salt was deemed necessary for the formation of the cationic 16-electron square planar Pd intermediate required for asymmetric induction. The counterion of the silver salt was found to have a significant effect on the optical yield, with phosphate providing optimal results due to its very low nucleophilicity. In contrast, Ag(OAc) results in almost racemic product due to attack at Pd by the nucleophilic acetate anion.



437b **438b** (54)

A similar series of alkenyl triflates **439** was prepared and tested in asymmetric Heck cyclizations.[220] Higher enantioselectivities were obtained than in the iodide variant without the need to add silver salts (Scheme 39). After a comprehensive screening, the optimal conditions were found to be 5 mol% $Pd(OAc)_2$, 10 mol% (*R*)-BINAP **341**, K_2CO_3 (2 M equivalents) with toluene or benzene as solvent.[221]



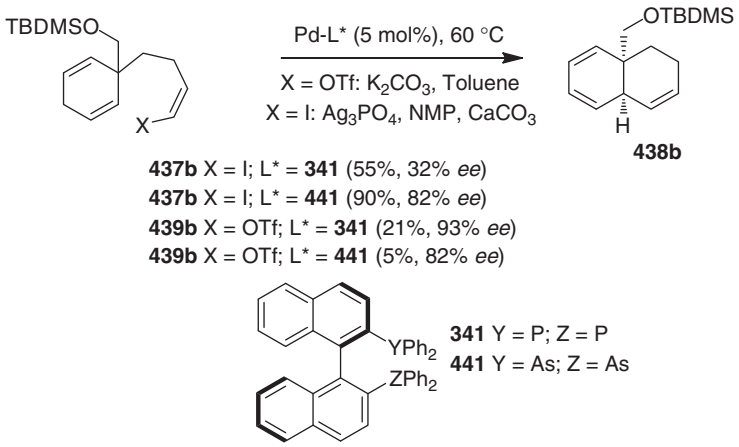
439a R = CO_2Me
439b R = $CH_2OTBDMS$
439c R = CH_2OAc
439d R = CH_2OPv

440a 54% yield, 91% *ee*
440b 35% yield, 92% *ee*
440c 44% yield, 89% *ee*
440d 60% yield, 91% *ee*

Scheme 39

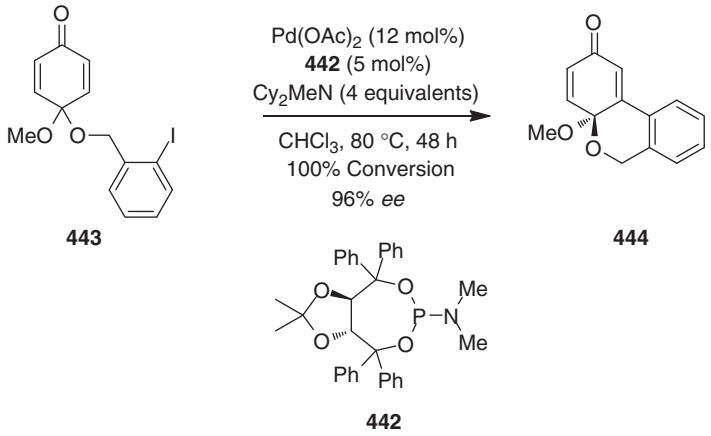
Since BINAP had proven to be the most effective ligand in the majority of systems investigated thus far, many of the new ligands developed for application in Heck chemistry were variations on the BINAP template. Shibasaki prepared a bisarsine

derivative, (R)-BINAs **441**, which compared favorably to BINAP in the cyclization of alkenyl iodides but performed less well for the analogous triflates (Scheme 40).[222]



Scheme 40

The phosphoramidite ligand **442**, developed by Feringa, is the only reported example to date of a monodentate ligand which has induced good enantioselectivities in the intramolecular asymmetric Heck cyclization of the cyclohexadienone **443** which proceeded in excellent yield (100% conversion, 48 h), affording **444** with an enantioselectivity of 96% (equation 55).[223] It is noteworthy that as the ligand system is monodentate, cationic Pd intermediates are not required for good enantioselectivity and therefore silver or thallium salts are not employed. The ligand to Pd ratio in the catalytically active species is as yet unknown but the authors speculate that two ligands are bound to the metal center.

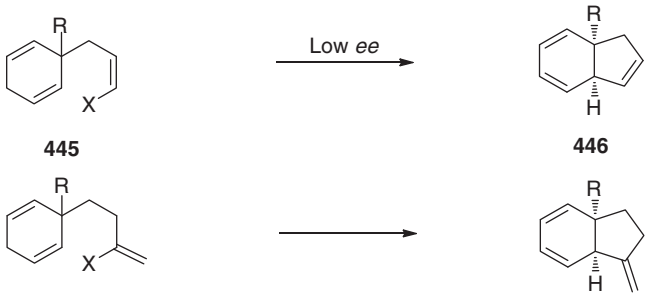


(55)

4.14.8.2.2 Asymmetric synthesis of hydrindans

The general method described for the synthesis of decalins has also been applied to the synthesis of the hydrindans.[224] Interestingly, the alkene geometry in the iodide or triflate substrate was crucial to the enantioselectivity obtained. Cyclization of the (*Z*)-alkene **445** resulted in almost racemic product **446** (<5% *ee*) (Scheme 41), whereas the intramolecular Heck reaction of alkene **447** afforded products **448** with good enantioselectivity under analogous reaction conditions. Contrary to the pattern seen with decalin systems, the alkenyl iodides provided cyclized products with higher *ee*s than the corresponding triflates.

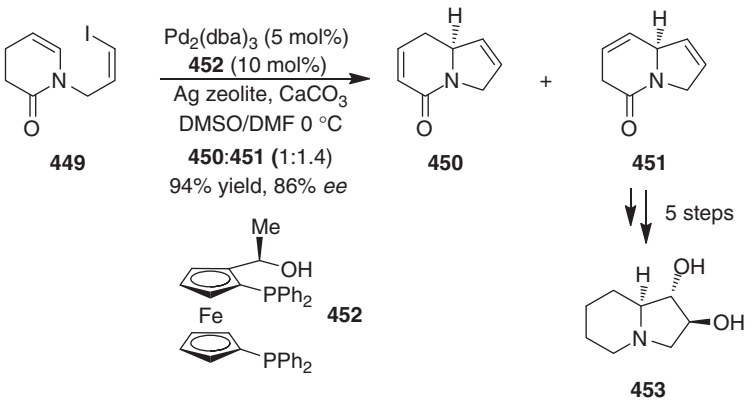
The hydrindan synthesis has been applied to the construction of enantio-enriched heterocyclic systems such as the indolizidines.[225] Cyclization of **449** resulted in a mixture of the desired indolizidine **450** and its double-bond isomer **451** in a combined 94% yield and 86% *ee* (Scheme 42). In contrast to carbocyclic systems, the ligand of choice was (*R*)-α-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl alcohol **452** and a Ag-exchanged zeolite proved superior to Ag_3PO_4. Indolizidine **451** may be quantitatively transformed to its double-bond isomer **450** and subsequently elaborated to the natural product lentiginosine **453**, a proven glycosidase inhibitor.[226]



X = I : [(*R*)-BINAP]-$PdCl_2$ (10 mol%), $CaCO_3$, Ag_3PO_4, NMP, 40 °C
X = OTf : $Pd(OAc)_2$ (5 mol%), (*R*)-BINAP (10 mol%), K_2CO_3, Benzene, 60 °C

447a R = CO_2Me; X = I — **448a** (73%, 83% *ee*)
447b R = CH_2Me; X = OTf — **448b** (63%, 73% *ee*)
447c R = CH_2OAc; X = I — **448c** (73%, 84% *ee*)
447d R = $CH_2OTBDMS$; X = I — **448d** (78%, 82% *ee*)

Scheme 41



Scheme 42

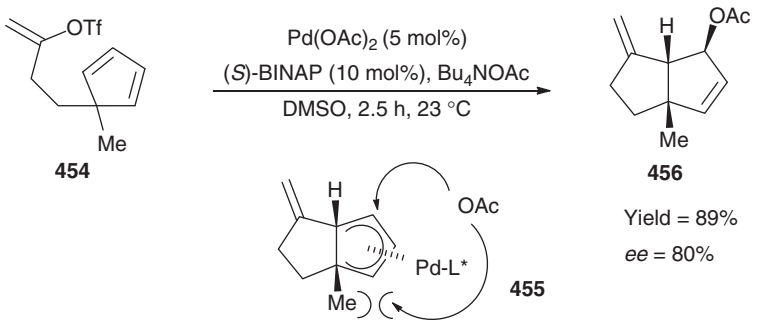
4.14.8.2.3 Asymmetric synthesis of diquinanes

The successful cyclizations for the formation of 6,6- and 6,5-ring systems suggested an extension of the methodology to the synthesis of 5,5-bicycles, which are common subunits in many natural products. The use of prochiral cyclopentadienyl systems results in the formation of a π-allyl Pd species which may be subsequently attacked by a nucleophile. This asymmetric Heck/allylic substitution cascade process allows for the construction of optically active bicyclic systems, which can be functionalized with a variety of nucleophiles (acetates or amines have most commonly been applied) in a regio- and stereocontrolled manner. As an example, the alkenyl triflate **454** was converted to the diquinane **456** via intermediate **455** in 89% yield and 80% *ee* when acetate was used as the nucleophile (Scheme 43).[227]

Carbon-based nucleophiles (mainly sodium enolates) have also been applied in this process and the Heck product **457** was subsequently elaborated to realize the first catalytic asymmetric total synthesis of the triquinane (–)-capnellene **458**, which possesses antibacterial and antitumor properties (Scheme 44).[228]

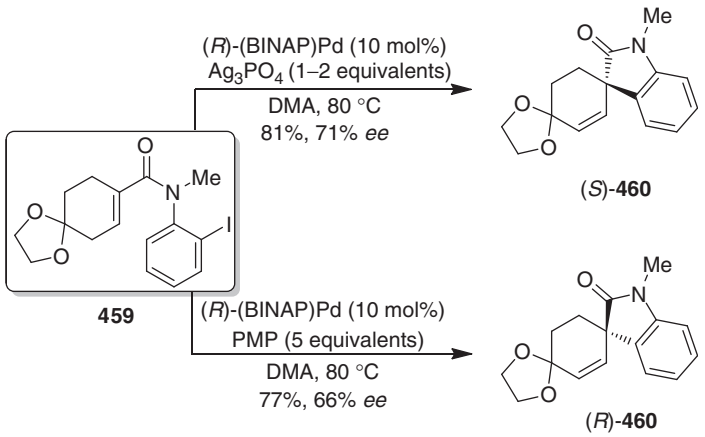
4.14.8.2.4 Asymmetric synthesis of quaternary carbon centers

The synthesis of quaternary carbon centers by asymmetric intramolecular Heck reactions has been extensively studied, particularly by the group of Overman. Their work focused mainly on the synthesis of spirocyclic heterocycles and encompassed mechanistic as well as purely synthetic investigations. The iodoenamide **459** was chosen for their initial studies as potential double-bond isomerization of the Heck reaction product **460** is avoided with this substrate. Various commercially available chiral chelating bisphosphines were tested with BINAP **341** proving most efficacious affording enantioselectivities up to 71% (Scheme 45).[229]



Scheme 43

Scheme 44

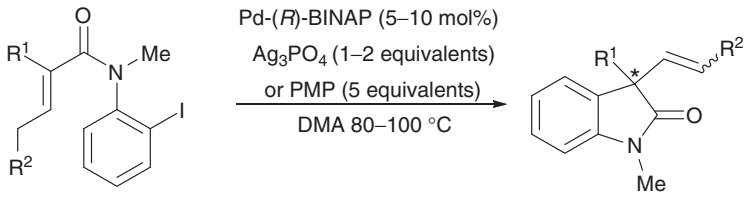


Scheme 45

Optimization studies revealed that enantioselectivities were highest using a catalyst system prepared in a polar solvent (*N*-methylpyrrolidine or *N*,*N*-dimethylacetamide), from BINAP **341** (10 mol%), $Pd_2(dba)_3$ (5 mol%) with either Ag_3PO_4 or Ag_2CO_3. Surprisingly, it was discovered that good enantioselectivity could be achieved in the absence of a silver salt and in the presence of the highly basic tertiary amine PMP. This was the first example of a Heck reaction proceeding with good asymmetric induction using iodo-precursors in the absence of a silver salt. Significantly, the products obtained under both sets of reaction conditions were enantiomeric, even though the same enantiomer of chiral ligand was used.

In a related study Overman also investigated the cyclization of acyclic alkenes to form quaternary centers under both neutral (iodide with PMP as base), and cationic conditions (iodide with added silver salt).[10b] Cyclization of the (*Z*)-iodoalkene series **461a–c** proceeded in good yields, generating the 3,3-disubstituted oxindoles **462a–c** (Scheme 46). When the α-substituent (R^1) was a methyl group, enantioselectivity was moderate under both cationic and neutral conditions. For the bulkier

α-substituents phenyl and *t*-butyl, enantioselectivity was good under cationic conditions but still remained low under neutral conditions. The terminal substituent did not appear to have a significant effect on stereoselectivity with similar results seen with hydrogen and the considerably more bulky silyl groups. Interestingly, the (*R*)-enantiomer of **462c** was generated under both cationic and neutral conditions which contrasts with the results obtained for the other compounds in this series.



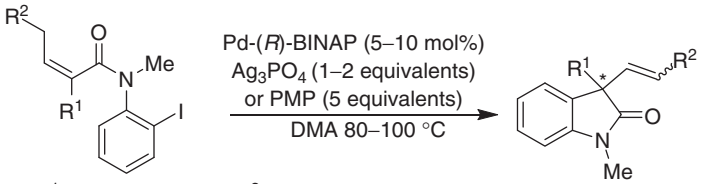
461a: R^1 = Me; R^2 = OTBDMS
461b: R^1 = Ph; R^2 = OTIPS
461c: R^1 = *t*-Bu; R^2 = OTIPS

462

PMP Conditions:	Ag_3PO_4 Conditions:
461a: 58% yield, 38% *ee* (*R*)	**461a**: 80% yield, 45% *ee* (*S*)
461b: 74% yield, 35% *ee* (*R*)	**461b**: 93% yield, 73% *ee* (*S*)
461c: 90% yield, 27% *ee* (*R*)	**461c**: 41% yield, 72% *ee* (*R*)

Scheme 46

The utility of the neutral pathway may be seen in the contrasting results achieved for the (*E*)-alkene series (**463a–c**) (Scheme 47). In this case the employment of neutral conditions (PMP) provided the product with greater enantioselectivity in the majority of cases. Enantioselectivities of >90% were obtained in some cases (**463a** and **463c**). When the solvent was changed to THF substrate **463c** was cyclized in good yield and with an excellent 97% *ee*. Substrates with bulky α-substituents gave moderate to low enantioselectivities under both sets of conditions (**463b**). In contrast to the related (*Z*)-substrates, the same enantiomer of cyclized product was synthesized under both sets of conditions, in all of the entries in this series.



463a $R^1 = CH_2CH(OMe)_2$; R^2 = OTBDMS
463b R^1 = Ph; R^2 = OTIPS
463c R^1 = Me; R^2 = OTBDMS

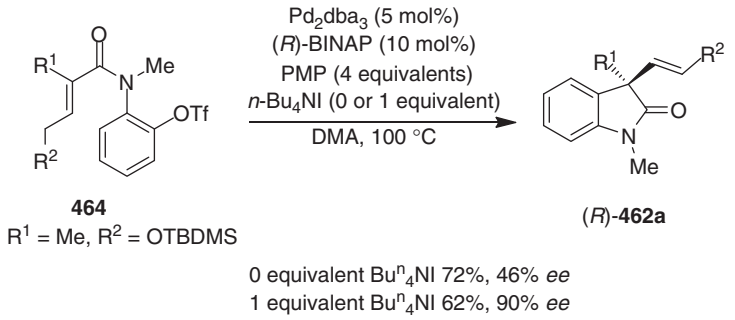
462

463a Additive = PMP, 93%, 91% *ee* (*S*)
463b Additive = Ag_3PO_4, 86%, 65% *ee* (*R*)
463b Additive = PMP, <5%, 19% *ee* (*R*)
463c Additive = PMP, 80%, 92% *ee* (*R*)

Scheme 47

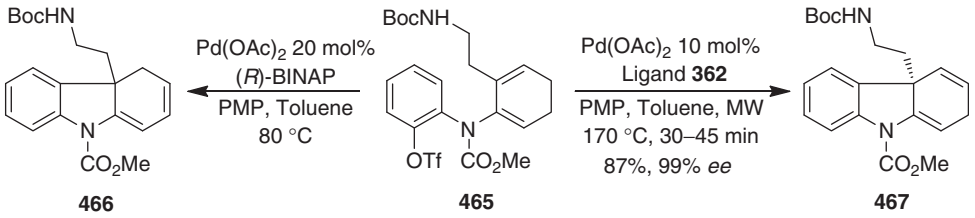
The analogous (*Z*)-aryl triflate **464** cyclized under cationic conditions giving the oxindole **462a** in 72% yield and 46% *ee*. Heck cyclizations of this substrate could be diverted down the more enantioselective (90% *ee*) neutral pathway by the addition of halide salts (Scheme 48).

An asymmetric intramolecular Heck reaction was carried out by Overman in their total synthesis of (+)-Minfiensine (Scheme 49).[230] Using $Pd(OAc)_2$/BINAP as the precatalyst, the reaction of **465** yielded **466**, a result of Pd-H-mediated isomerization of the initially formed product **467**. Attempts to minimize double-bond migration by using a stronger base or a larger excess of base were unsuccessful.[231] PHOX ligands are known from intermolecular asymmetric Heck chemistry to effect minimal double-bond migration.[232] When using a Pd complex of PHOX ligand **362**, the desired product **467**



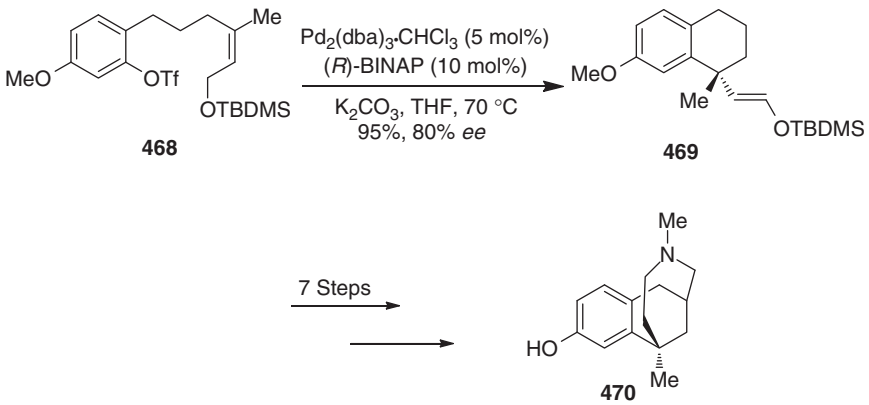
Scheme 48

was obtained in up 87% yield and 99% *ee*. The long reaction time (70 h) was successfully reduced to 30–45 min under MW irradiation without a reduction in yield or enantioselectivity, and additionally allowed for a reduction in catalyst loading of Pd/C to 10%.



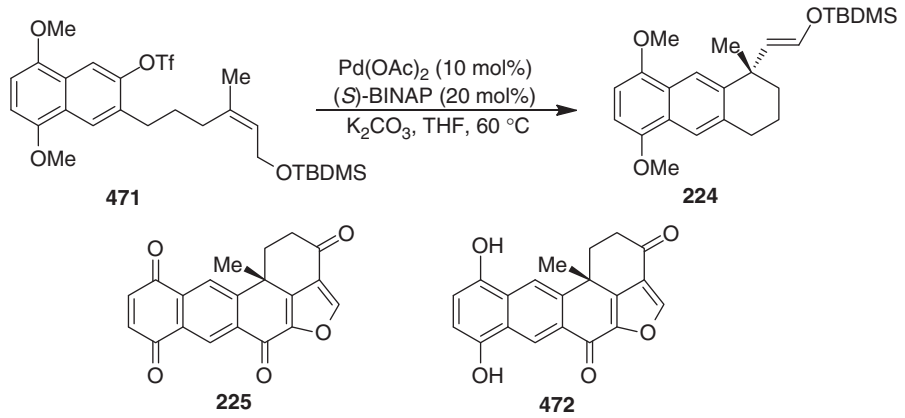
Scheme 49

Shibasaki has also examined the formation of chiral benzylic quaternary centers on tetralin type systems.[233] As is the case for many asymmetric Heck cyclizations, a pronounced geometry effect on stereoinduction was apparent. Whereas the (*Z*)-alkene **468** cyclized with an enantioselectivity of 80%, forming the tetralin **469** in 95% yield, the corresponding (*E*)-alkene reacted in similar yield but with an enantioselectivity of just 51%. This process was extended to the asymmetric synthesis of the analgesic (–)-eptazocine **470** (Scheme 50).



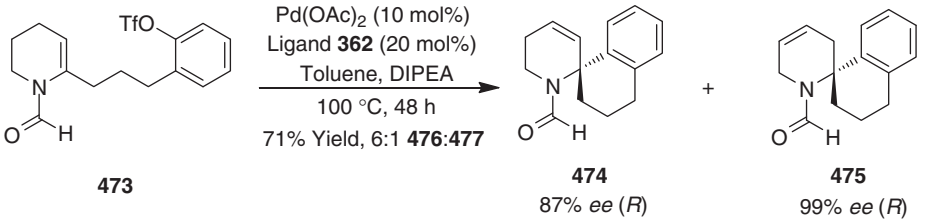
Scheme 50

A related naphthyl triflate **471** was cyclized in 78% yield and 87% *ee* under similar conditions indicating that the nature of the aryl group did not significantly affect the outcome. The Heck product, **224**, was converted in several steps to the natural products, halenaquinone **225** and halenaquinol **472** (equation 56).[234]



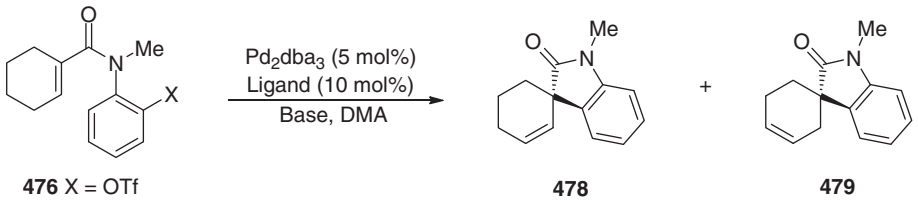
(56)

The diphenylphosphinooxazoline ligands were the first class of bidentate phosphinamine ligands that showed significant promise in asymmetric intramolecular Heck chemistry. Cyclization of the triflate **473** proceeded in an overall yield of 71% affording the double-bond isomers **474** and **475** in enantioselectivities of 87% and 99%, respectively. Employing ligand **362** (equation 57).[235] The same procedure using a Pd-BINAP-derived catalyst produced a more complex mixture of products in lower enantioselectivity. This was the first published example of an enantioselective intramolecular Heck reaction with a bidentate phosphinamine ligand that proved to be superior to BINAP.

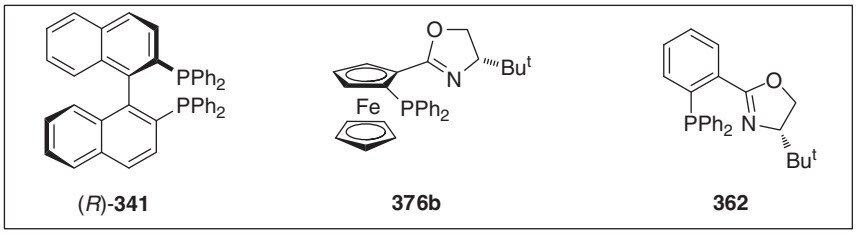


(57)

The success of heterobidentate P–N ligands **362** and **376** in the intermolecular variant of the Heck reaction prompted Guiry to investigate their use in intramolecular asymmetric Heck chemistry.[236] They studied the cyclization of the novel triflate **476**, readily prepared in five steps from 1-cyclohexene-1-carboxylic acid, as it provided a useful comparison with the neutral pathway studied by Overman with the analogous aryl iodide **477** as substrate (**Scheme 51**).[237] The optimum enantioselectivity obtained was 85% employing the *t*-leucinol-derived ferrocenyloxazoline ligand **376b**. The isomer distribution of the product spirooxindoles was



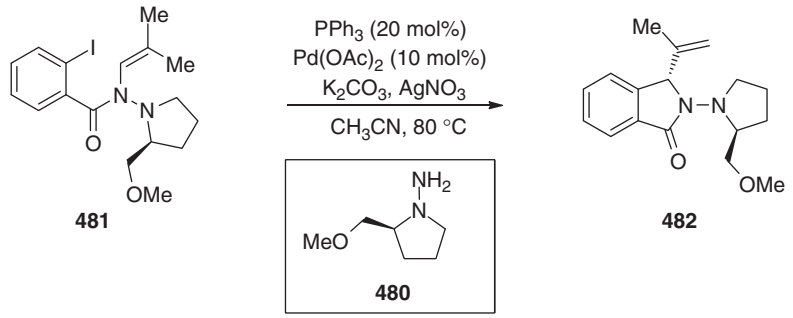
Ligand = **341**; Base = PMP **478**:**479** = 25:75, 90%, *ee* = 74% (*S*)
Ligand = **376b**; Base = PS **478**:**479** = 99:1, 30%, *ee* = 85% (*R*)
Ligand = **362**; Base = PS **478**:**479** = 99: 1, 20%, *ee* = 71% (*R*)



Scheme 51

dependent on the ligand chosen, with the oxazoline-containing ligands showing an increased selectivity (up to 99:1) for the $\Delta^{2,3}$-isomer **478** compared with BINAP **341** (optimum 75:25).

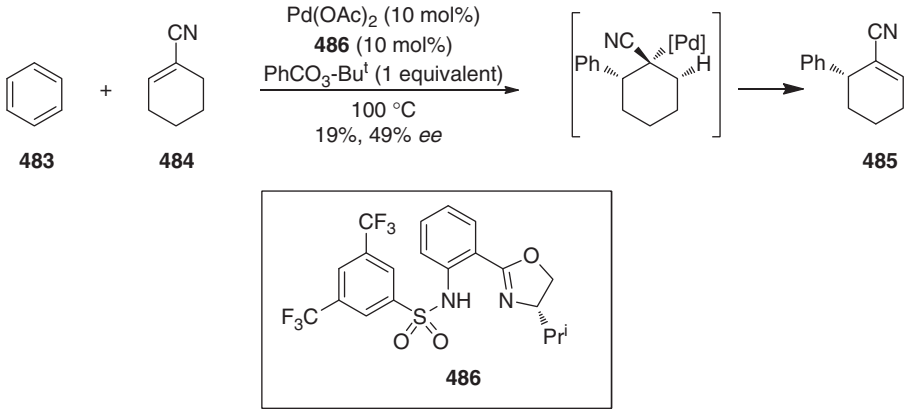
The use of chiral auxiliaries is another strategy that has been applied with some success in asymmetric intramolecular Heck chemistry. An example of an auxiliary-promoted intramolecular Heck reaction was reported by Grigg using (*S*)-1-amino-2-(methoxymethyl)pyrrolidine **480** (equation 58).[89] Excellent diastereoselectivity (>95% *de*) was obtained in the cyclization of **481** to **482**. The drawbacks of this approach, as with all auxiliary chemistry, are the extra chemical steps involved in attaching and removing the auxiliary.



(58)

4.14.8.3 The Asymmetric Fujiwara–Moritani Reaction

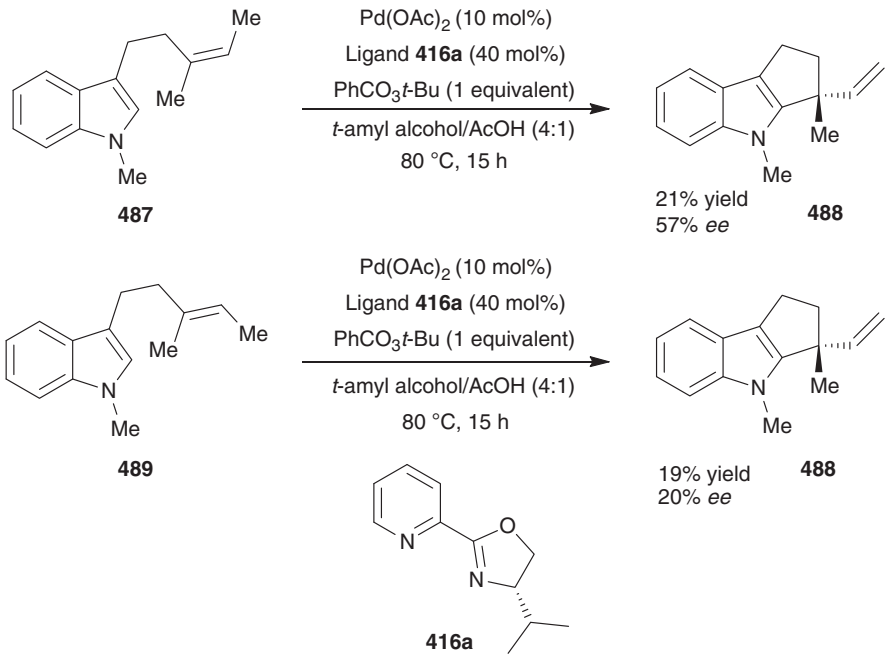
The asymmetric version of the Fujiwara–Moritani reaction (Sections 4.14.7.1–4.14.7.6) remains poorly developed due to the reaction's inherent tendency to form a sp^2 center via β-hydride elimination (**282** to **283**, Scheme 21). The only example of an intermolecular asymmetric Fujiwara–Moritani reaction was reported by Mikami, who obtained a chiral product **485** from the reaction of benzene **483** with cyclic olefin **484** (equation 59).[238] The initially formed chiral center is retained as β-hydride elimination occurs at the β-carbon not involved in the initial migratory insertion, as in the standard intermolecular asymmetric Heck reaction. The mixing of ligand **486** with an equimolar amount of $Pd(OAc)_2$ provided a crystalline Pd(II) complex, which when applied to benzene and cyclohexenecarbonitrile under otherwise identical conditions produced no reaction. Addition of achiral $Pd(OAc)_2$ provided the desired product in 30% yield and 30% *ee*. It is therefore thought that the active catalytic species is a 1:1 complex of the chiral ligand Pd(II) complex and $Pd(OAc)_2$.



(59)

Oestreich reported the first asymmetric intramolecular Fujiwara–Moritani reaction, applying a range of modified PyOX ligands, optimal for ligand **416a**, to a substrate developed by Stoltz for the racemic intramolecular Fujiwara–Moritani reaction (Scheme 52).[239] The levels of enantioselectivity were substantially different for the (*Z*)- and (*E*)- isomers **487** and **489** at 57% and 20% *ee*, respectively.

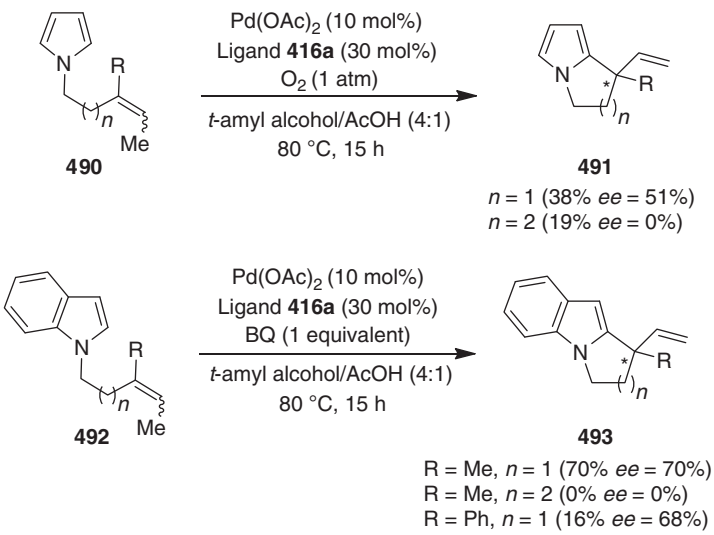
This was the starting point for the synthesis of a range of *N,N* oxazoline-containing ligands (PyOX ligands) by Oestreich. Changing the reoxidant for the reaction affected the enantioselectivity and yield, with 1 atm. of O_2 producing the best results in combination with ligand **416a** (65% yield, 39% *ee*, stereoisomeric mixture of **487** and **489**). The best



Scheme 52

overall result was using ligand **416a** and 1,4-BQ as a reoxidant, providing 71% yield and 54% *ee* when using the **487** as the substrate.

Oestreich subsequently carried out a more detailed investigation on the application of ligands **416a–e** to the asymmetric intramolecular Fujiwara–Moritani reaction.[240] Ligand **416a** proved superior when applied to a range of indole and pyrrole substrates (Scheme 53), with the highest enantioselectivities reported for the intramolecular Fujiwara–Moritani reaction reported to date. It is notable that when the ring was expanded by one carbon, conversion dropped sharply and enantioselectivity was almost completely absent. The reasons for such drastic differences between the 5- and 6-*exo-trig* annulations are not presently understood.



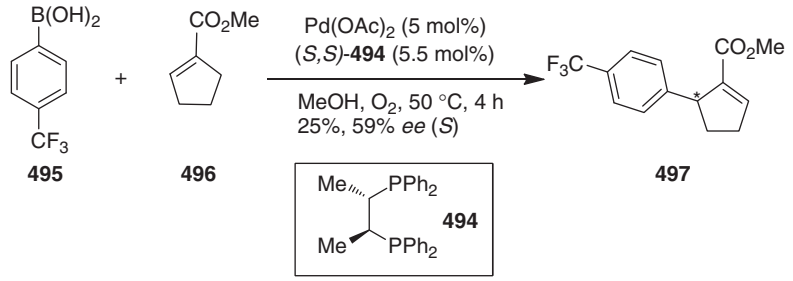
Scheme 53

There is certainly scope for further work on the asymmetric Fujiwara–Moritani reaction, which remains surprisingly poorly developed. The influence of reoxidant on enantioselectivity and the effect of ring size in the case of the intramolecular variant merit further investigations.

4.14.8.4 Asymmetric Oxidative Boron Heck-type Reactions

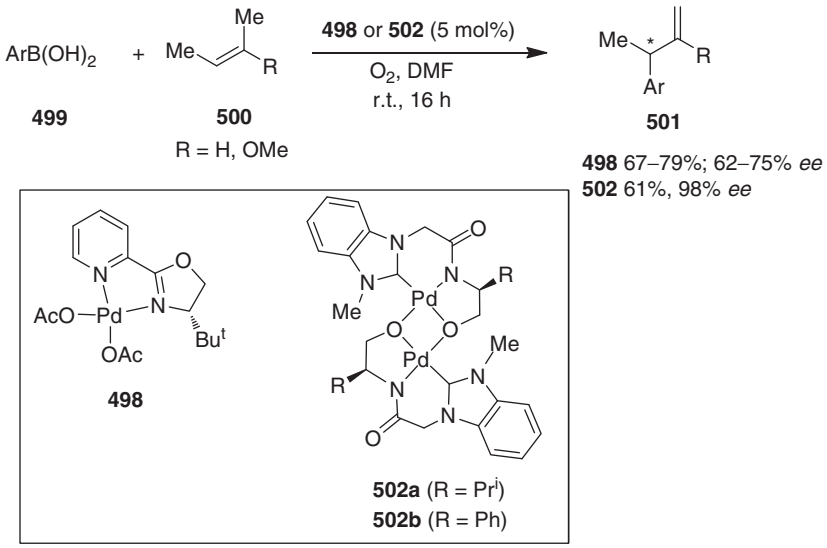
In contrast to the asymmetric Fujiwara–Moritani reaction, which remains poorly developed, there have been promising recent developments of the oxidative Pd(II)-catalyzed boron Heck-type reaction.[241] Mechanistically similar to the Fujiwara–Moritani reaction, it proceeds *via* transmetallation as opposed to C–H activation.[242] The nonenantioselective version of this reaction was first reported by Heck in 1975 using stoichiometric $Pd(OAc)_2$, however it has only recently been developed as an asymmetric process.[243] It is an attractive reaction as in the absence of a halogen–Pd intermediate the reaction is more likely to proceed *via* the cationic route, which is important for enantioselectivity.[244]

The first report of a Pd(II)-catalyzed organoboron-mediated Heck-type reaction was by Mikami, who applied a $Pd(OAc)_2$/(S,S)-Chiraphos **494** catalytic system to a range of cyclopentenecarboxylates **496** using several substituted phenylboronic acids **495**.[242] The reactions proceeded with poor-to-moderate yields and enantioselectivities, achieving up to 59% *ee* of the (*S*) product **497** in 25% yield (equation 60).



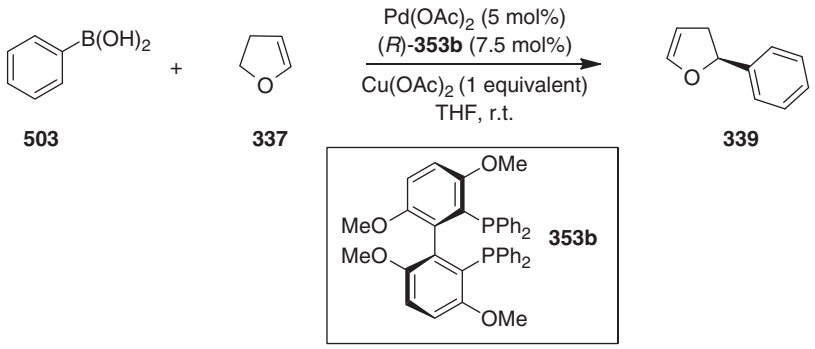
(60)

Jung reported the application of the Pd(II) complex **498** to the intermolecular coupling of arylboronic acid **499** with acyclic alkene **500**, which are challenging substrates for this type of reaction (**Scheme 54**).[245] Good yields (67–76%) and enantiomeric excess (62–75%) were obtained under milder conditions (noninert atmosphere and room temperature) compared with conventional Heck-type reactions. They subsequently described the efficient synthesis from chiral amino acids of novel chiral Pd(II) complexes **502** possessing a tridentate NHC amidate alkoxide ligand.[246] In the oxidative boron Heck-type reaction of **499** and **500**, both dimers provided excellent enantioselectivities (*ee*s of up to 98%) and moderate-to-good yields (up to 61%) of **501**.



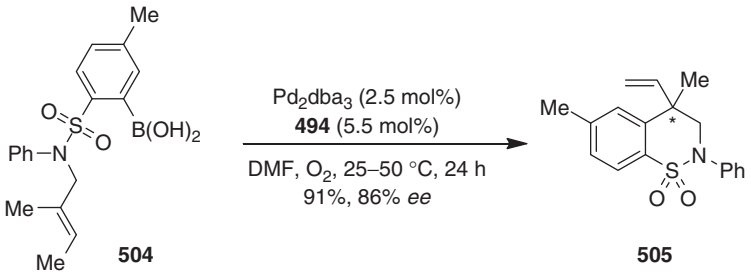
Scheme 54

An important contribution to the reaction was more recently reported by Gelman and coworkers, who found that the reaction could be carried out under air-free conditions without base at room temperature when using $Cu(OAc)_2$ as a stoichiometric reoxidant.[244] Using (*R*)-MeOBIPHEP **353b** as the ligand, the phenylation of 2,3-dihydrofuran **337** was achieved in 63% yield and 83% *ee* (equation 61).



(61)

The first and only example of an intramolecular oxidative boron Heck-type reaction was reported by Mikami, who used the Pd_2dba_3/(S,S)-Chiraphos **494** catalytic system to facilitate the synthesis of chiral quaternary carbon centers via ring closure of a sulfonamide species **504**. Yields and enantioselectivities for sulfonamide **505** of up to 91% and 86%, respectively were obtained (equation 62).[247]



(62)

4.14.9 Combinatorial and Solid-Phase Syntheses

Solid-phase synthesis, first developed in the 1960's by Merrifield for use in peptide synthesis,[248] has many advantages over conventional solution chemistry. These include the easy purification by filtration of the reaction mixture to remove any unreacted starting material and the ability to use excess reagents. This technology can also be applied in transition metal mediated cross-coupling reactions including the Heck reaction.[249]

4.14.9.1 Solid Supports in the Heck Reaction

The use of the Heck reaction as part of a solid-phase synthesis requires the attachment of at least one reaction component to the solid support. In this regard there are two options for an intermolecular Heck reaction: (a) the olefin or (b) the aryl species.

The requirements for a suitable solid support are primarily that the linker joining the solid support to the target must be stable to the reaction conditions and easily cleaved to release the target molecule at the end of the reaction.

Although most solid supports used in solid-phase synthesis are polystyrenes, pyrrole immobilized on graphite has also been used in a solid-phase Heck reaction.[250]

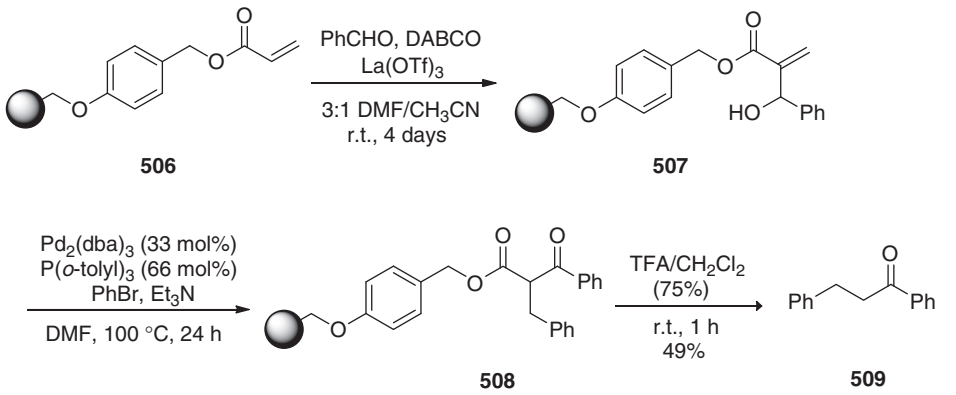
4.14.9.2 Immobilization of the Olefin on a Solid Support

Ganesan employed solid-phase chemistry in the synthesis of aryl ketones, using the Baylis–Hillman and Heck reactions.[251] They used the Wang resin as the product could be easily cleaved with acid. Cleavage resulted in release of the β-keto acids which then lost CO_2 to give the aryl ketone product (Scheme 55).

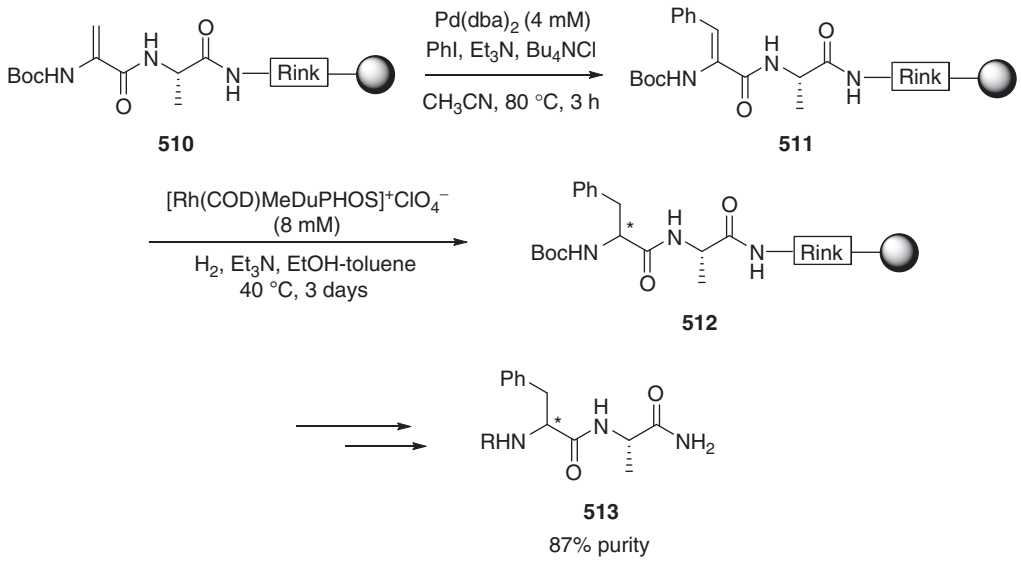
In the optimization of the reaction it was found that a mixture of DMF and CH_3CN was best as DMF is required for optimum swelling of the polystyrene resin and the catalyst was not effective in neat DMF. $Pd_2(dba)_3$, was used as $Pd(OAc)_2$ was found to be unsuitable for the reaction.

Takahashi performed a solid-supported Heck reaction in their synthesis of peptides containing nonnatural amino acids.[252] The Rink amide linker was used in their synthesis and the Heck reaction was used to introduce an aryl group as the amino acid side chain. The alkene was then asymmetrically reduced to form amino acids with an unnatural side chain (Scheme 56).

The optimal conditions for the Heck reaction were found to be $Pd(dba)_2$, Bu_4NCl, and Et_3N as the base in CH_3CN.



Scheme 55



Scheme 56

4.14.9.3 Immobilization of the Aryl Halide on a Solid Support

Ruhland employed the Heck reaction in the synthesis of functionalized β-lactams to investigate their potential as pharmaceuticals.[253] The investigations into the synthesis of the β-lactams involved the use of a Suzuki cross-coupling reaction to synthesize biaryl derivatives and use of the Heck reaction to form the styryl-substituted products (Figure 22).

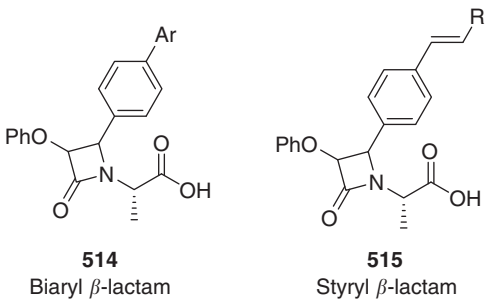
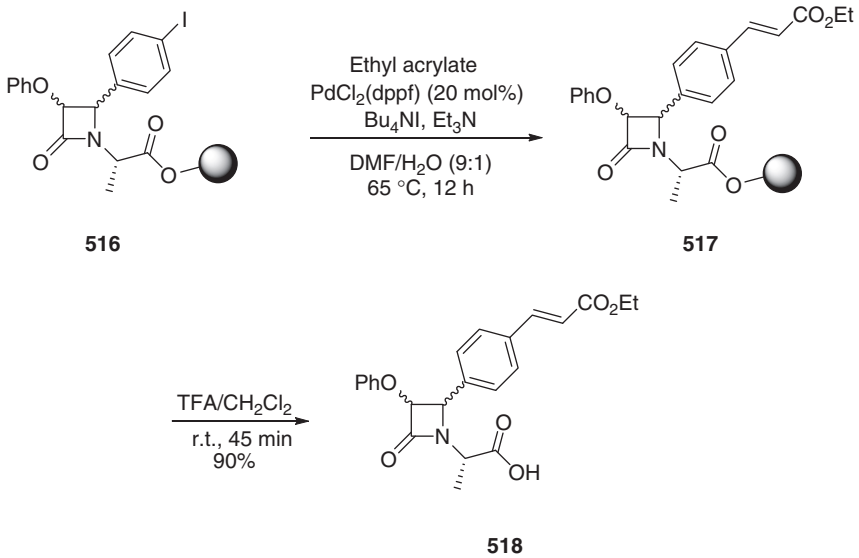


Figure 22 β-Lactams synthesised via combinatorial chemistry.

Their studies investigated the use of both the Sasrin and the Wang resin as solid-supports for the synthesis. The synthesis involved a [2 + 2] cycloaddition to form the core β-lactam structure. On performing the C–C bond forming reaction it was found

that common conditions for the Heck reaction such as $Pd(OAc)_2/PPh_3/K_2CO_3$ and also $Pd(OAc)_2/P(o\text{-tolyl})_3/NEt_3$ were both unsuccessful. They found $PdCl_2$(dppf) in the presence of Bu_4NI and Et_3N in a DMF/H_2O mixture to be a suitable precatalyst for the reaction (Scheme 57).

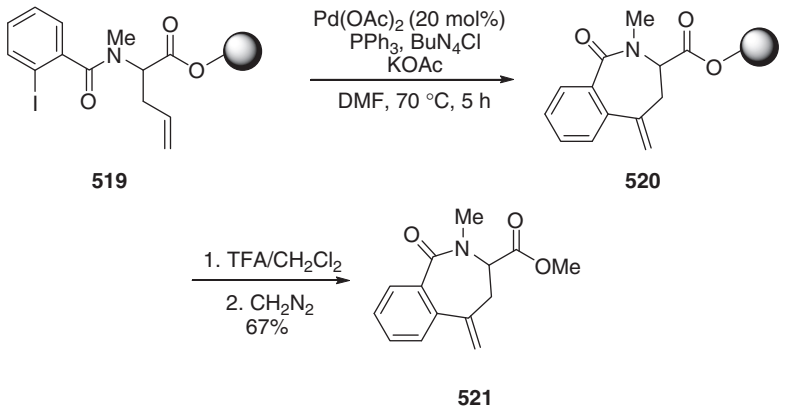


516 517 518

Scheme 57

4.14.9.4 Intramolecular Heck Reactions on a Solid Support

Bolton used solid-phase synthesis for the 7-*exo* cyclization of 2-iodobenzene-tethered allyl or propargyl glycines in the formation of the corresponding benzazepines.[254] In the synthesis of the benzaepine **251**, following the Heck reaction the product was cleaved to give the carboxylic acid which was then converted to the methyl ester. The Heck reaction was performed using the Jeffrey conditions (Scheme 58). The overall yield of the solid-phase process was 67% from the initial attachment and manipulation of the aryl group (eight steps).

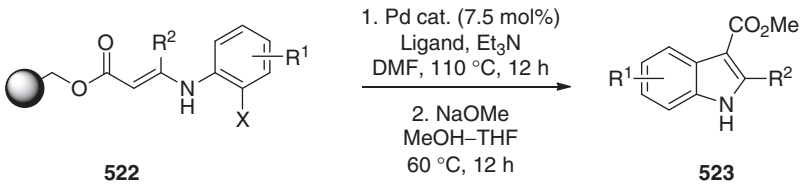


519 520 521

Scheme 58

Kondo used an intramolecular Heck reaction in the synthesis of indoles and related heterocyclic compounds.[255] The linker used in the synthesis had to be acid stable as one of the steps in the sequence required the use of acid. The polystyrene resin contained hydroxy groups which allowed addition of the substrate to the solid support. Cleavage at the end of the synthesis was achieved through *trans*-esterification using sodium methoxide in methanol. An enaminoester **522** was the substrate for the intramolecular Heck reaction (Table 19). The palladium source used was either $Pd(OAc)_2$ or $Pd_2(dba)_3$, with $P(o\text{-tolyl})_3$ as the ligand. In all of the examples reported the yields were good to moderate (27–78%), with $Pd_2(dba)_3$ better for aryl bromide substrates than $Pd(OAc)_2$.

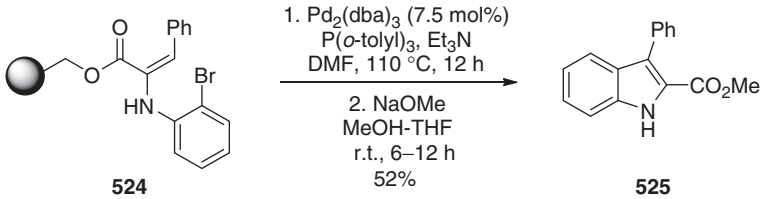
Table 19 Synthesis of indoles on a solid support



522 **523**

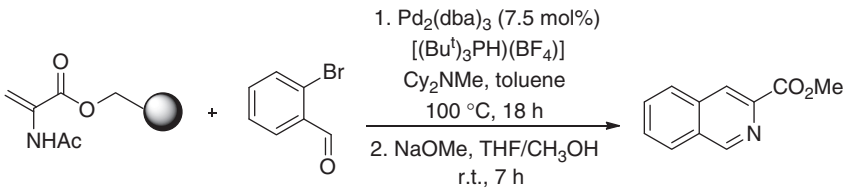
Entry	*X*	*R*^{1}	*R*^{2}	*Pd source*	*Ligand*	*Yield (%)*
1	I	H	Me	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	63
2	Br	5-Me	Me	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	43
3	Br	6-CF_3	Me	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	32
4	I	H	H	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	78
5	Br	6-NO_2	H	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	39
6	Br	6-CF_3	H	$Pd_2(dba)_3$	P(*o*-tolyl)$_3$	66

3-Substituted indole 2-carboxylates **525** were synthesized in a similar fashion by Kondo using an isomeric enaminoester (equation 63).



524 **525** (63)

Their methodology was also applied to the synthesis of a substituted isoquinoline **528** in 56% yield (equation 64).



526 **527** **528** (64)

4.14.9.5 Traceless Linkers

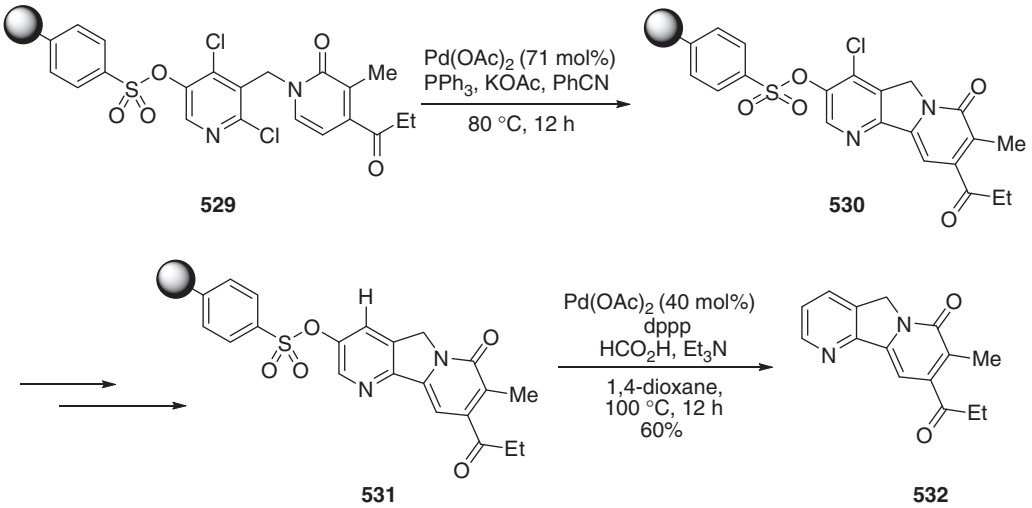
The use of resins such as the Wang and the Rink resin leaves a functional group behind following cleavage from the solid support. This can give rise to difficulties if the functionality is not wanted in the product and cannot easily be converted into an alternative group. Therefore the development of a linker that does not leave a functional group following cleavage was desirable.

Kondo recently employed the use of a traceless linker in the synthesis of a mappicine ketone library.[256] The linker was attached to a JandaJel^{TM} resin. $Pd(OAc)_2$, PPh_3, and KOAc were used in a regioselective Heck reaction. The linker was then reductively cleaved using Pd catalysis at the end of the reaction leaving a hydrogen in place of the benzenesulfonate linker. As an example, the total yield of the mappicine ketone analog **532** at the end of the solid-phase sequence was 60% (Scheme 59).

4.14.10 New Reaction Media and Heating Techniques in the Heck Reaction

4.14.10.1 Introduction

The importance and versatility of the Heck reaction has led to the development of a number of nonclassical reaction techniques and methodologies. These aim to expand the utility and increase the efficiency of the Heck reaction by designing recyclable catalytic systems, by using of more environmentally benign reaction media and by using different heating techniques to speed up processing times.



Scheme 59

4.14.10.2 Ionic Liquids

ILs are salts which have a melting point below the boiling point of water with a very large liquidus range. They are liquid electrolytes that show a partially covalent structure. The most common IL comprises of an imidazolium, pyridinium, alkylammonium, or alkylphosphonium cation with an inorganic polyatomic anion such as BF_4^- and PF_6^-. They are capable of dissolving a variety of compounds, in particular transition metal catalysts, are nonvolatile, are potentially recyclable and display limited miscibility in organic solvents, opening up new opportunities for biphasic catalysis. Their use and popularity in organic synthesis and catalysis has been well documented.[257]

Solvents can have a profound effect on organic transformations and ILs are no exception. ILs have been widely utilized in the Heck reaction since the seminal work in the area by Kaufmann in 1996 and the topic has been covered in a number of reviews.[258] Kaufmann reported the Heck reaction of bromobenzene with *n*-butyl acrylate using a Pd(0) precursor in a molten tetraalkylphosphonium bromide salt and Et_3N in very high yields without the requirement for additional phosphine ligands.[259] The catalyst system could be recycled for several runs and the authors suggest a stabilizing effect of the IL on the Pd catalyst.

Herrmann and Böhm, through extensive studies, showed clear advantages of ILs over conventional organic solvents, particularly for aryl chloride substrates. The Hermann–Beller palladacycle (**36**, Figure 8) catalyst system showed increased activation and stabilization in Bu_4NBr. For example, the yield for the coupling of bromobenzene and styrene increased from 20% in DMF to >99% in Bu_4NBr.[260] The use of certain imidazolium-based ILs creates the possibility to form *in situ* Pd–carbene complexes.[261] Preformed carbene complexes have also been utilized for Heck reactions in ILs.[262] ILs have also been successfully applied in a number of ligand-free protocols with $Pd(OAc)_2$, $PdCl_2$ or Pd/C.[263] A number of these systems showed excellent regioselectivity and this is due to the ability of the IL to act as a halide scavenger and promote the cationic reaction pathway.[264] ILs are also useful solvents for supported Pd-catalysts and Pd-nanoparticles.[17a,265]

4.14.10.3 Fluorous Solvent and Catalysts

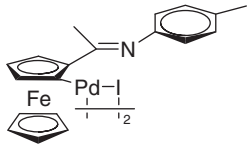
Since the first systematic use of perfluorinated solvents and catalysts in organic synthesis,[266] their application has gained in popularity due to their chemical inertness, nonflammability, thermal stability, and nontoxic nature.[267] They are immiscible with most organic solvents at ambient temperature but are miscible at higher temperatures. This offers the possibility to easily separate any fluorous-containing component, such as a catalyst, from the organic product by a simple fluorous/organic phase separation at room temperature, following a one-phase reaction at elevated temperature. Fluorous solvents have been utilized in the Heck reaction since the first report by Sinou and the area has been reviewed on previous occasions.[258b,268] The most common fluorous solvents used are perfloroalkanes, perfluorotrialkylamines, and perfluorodialkyl ethers. A Pd salt can be combined with a reaction component containing a fluorous tag to increase solubility of the catalyst, such as a perfluorinated ligand[268b,269] or perfluorinated DMF.[270] The use of preformed perfluorinated Pd-complexes has also been demonstrated.[271] Perfluorinated solvents are also suitable for Heck reactions catalyzed by Pd nanoparticles.[269f,272] The Heck reaction has been shown to proceed successfully using perfluorinated solvents, catalysts or ligands, however, these compounds are expensive and extraction and recycling of the fluorous catalyst is not always straightforward and may require purification using a fluorous silica gel, which limits its advantages. It should also be noted that processing of deactivated aryl chlorides in fluorous media has yet to be reported.

4.14.10.4 Supercritical Fluids

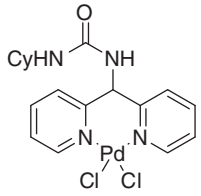
Supercritical fluids (SCFs), such as supercritical CO_2 ($scCO_2$) and water (scH_2O), have long been utilized in large-scale industrial processes for extraction and chromatography.[273] $ScCO_2$ has become increasingly popular as a solvent for modern organic synthesis as it is inexpensive, readily available, nontoxic, environmentally friendly, can form a single-phase mixture with gaseous reactants and has tunable properties by variation of temperature and pressure (critical temperature, $T_c = 31\ ^\circ C$, critical pressure, $P_c = 73$ atm). ScH_2O has also been utilized as it behaves like many organic solvents at or near critical temperature, however, the conditions ($T_c = 374\ ^\circ C$ and $P_c = 218$ atm) are harsh and it can participate in chemical transformations, unlike $scCO_2$. ScH_2O was first applied to the Heck reaction of iodobenzene and styrene which afforded up to 30% yield. More significantly, independent reports by Holmes and Tumas reported the coupling of iodobenzene with methyl acrylate in 91% yield and 94% conversion, respectively, using fluorinated phosphine ligands.[274] Highly fluorinated compounds have a very high solubility in $scCO_2$ and further applications in Heck reactions generally involved the use of fluorinated ligands.[275] For most systems, results of coupling in $scCO_2$ are comparable to those obtained in conventional organic solvents.[275b] $ScCO_2$ has demonstrated an ability to suppress double-bond migration in an intramolecular Heck cyclization in comparison to conventional solvents.[276] $ScCO_2$ has been successfully used in multiphase catalysis[277] and with heterogeneous,[278] supported[279] and encapsulated[280] catalysts and reagents. Despite the recent advances in the use of $scCO_2$ in the Heck reaction, the substrate scope is generally limited to aryl iodides, although aryl bromides and activated aryl chlorides have also been used.[277c,279b,281]

4.14.10.5 Aqueous Systems

The Heck reaction has been successfully carried out in aqueous systems of neat water or with additional organic solvent. This area has been extensively discussed in a number of reviews and book chapters to date.[258b,268c,282] Most systems use neat water in combination with a phase transfer catalyst (PTC) such as Bu_4NBr,[283] polyethylene glycol (PEG),[284] Amberlite IRA-400,[285] or a surfactant such as *N*-hexadecyl-*N*,*N*-dimethyl-3-ammonio-1-propanesulfonate (HDAPS)[286] and avoid the use of phosphine ligands. Two palladacycles (Figure 23), a ferrocenyl imine **533** and a dipyridylmethylamine **534** have been used with very low Pd concentrations of 0.0025 and 0.001 mol%, respectively.[287] Similarly, a supported oxime palladacycle, showed higher activity in neat water compared with DMF at a concentration of 0.001 mol%.[288] A number of systems containing water-soluble phosphine ligands have been designed such as triphenylphosphine trisulfonate (TPPTS)[289] and other water soluble phosphine salts.[290] These systems are usually aqueous biphasic reaction mixtures with polar organic solvents such as DMF or CH_3CN. In general aryl bromides are at least required for Heck reactions in aqueous systems; however, some activated aryl chlorides have been successfully employed.[287b,291]



533



534

Figure 23 Palladacycle catalysts for the Heck reaction in aqueous systems.

4.14.10.6 Ultrasound Irradiation

Ultrasound (US) is defined as sound waves between a frequency of 20 and several hundred megahertz, not energetic enough to directly promote a chemical reaction. However, the irradiation of a solution with US leads to formation of compressions and rarefactions, resulting in cavities, which in turn form collapsing microbubbles releasing large amounts of energy causing a huge increase in local temperature and pressure. There are few reports to date of the application of US to the Heck reaction. A first report applied US to *in situ* reduction of Pd(II) salts to form Pd(0) metallic clusters shown to be active in the Heck reaction of bromobenzene and styrene with only 30% conversion.[292] US was successfully applied for the Heck reaction in ILs using Pd–carbene complexes or Pd-nanoparticles at ambient temperature for the coupling of aryl iodides with acrylates and styrene.[293] The US-promoted Heck reaction catalyzed by Pd/C in NMP,[294] Pd-nanoparticles and Pd $(OAc)_2$ under aqueous conditions,[295] and using immobilized aryl halides as substrates[296] have been disclosed.

4.14.10.7 Microwave Irradiation

The use of MWs in organic synthesis has gained a huge amount of popularity in recent years due to their ability to drastically reduce reaction times.[297] The use of solvents with a permanent dipole is necessary to take advantage of this heating technique and

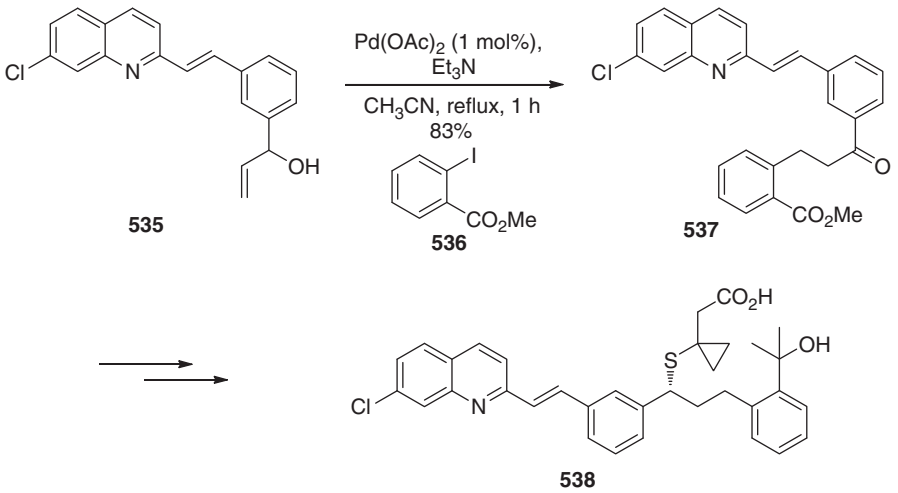
thus polar solvents such as DMF, acetonitrile, and water, popular Heck reaction solvents are required. The first MW-assisted Heck reaction was reported by Larhed in 1996, showing similar product patterns compared to conventional thermal heating, for a limited number of aryl iodides and bromides as substrates using Pd salts, with and without phosphine ligands.[298] Since then, MW-promoted Heck reactions have been carried out in water with PTCs[299] or with water-soluble ligands, using other ligand-free protocols,[300] in heterogeneous and solid supported systems[301] and in ILs.[263d,302] The coupling of activated and deactivated aryl chlorides was achieved with recyclable nano-Pd immobilized layered double hydroxide (LDH-Pd(0)) under MW-irradiation with high TOFs. For example, the coupling of 4-chloroanisole and styrene was accomplished in 1 h and 80% yield compared with over 40 h and 76% yield under thermal conditions.[303] The Heck coupling of 4-bromoanisole with *n*-butyl acrylate in the IL 1-butyl-3-methylimidazolium-PF_6, with $PdCl_2$ and P(*o*-tolyl)$_3$, afforded 99% conversion in 45 min.[304] The same reaction was carried out with water, in the presence of Bu_4NBr, in 80% yield with a very low Pd loading of 0.0009 mol%.[305] Heck couplings have also been carried out under simultaneous MW/US irradiation, an example being the coupling of 4-bromoacetophenone with styrene under ligand-free $Pd(OAc)_2$ conditions, which showed a marked improvement in yield over MW heating alone, 99% versus 87%, respectively.[306]

4.14.11 Natural Products and Active Pharmaceutical Ingredients

Both the intramolecular and intermolecular variants of the Heck reaction have been employed in the synthesis of natural products and active pharmaceutical ingredients. In this section selected examples will be discussed in order to highlight the use of the Heck reaction as a key step in total synthesis.

4.14.11.1 Industrial Application – Singulair®

Singulair® (**538**) is a trademarked drug produced by Merck & Co., Inc. for the treatment of prophylaxis and chronic-asthma.[307] The synthesis of this selective leukotriene receptor antagonist employs the Heck reaction to couple the two key fragments **535** and **536** of the molecule (Scheme 60).[308]



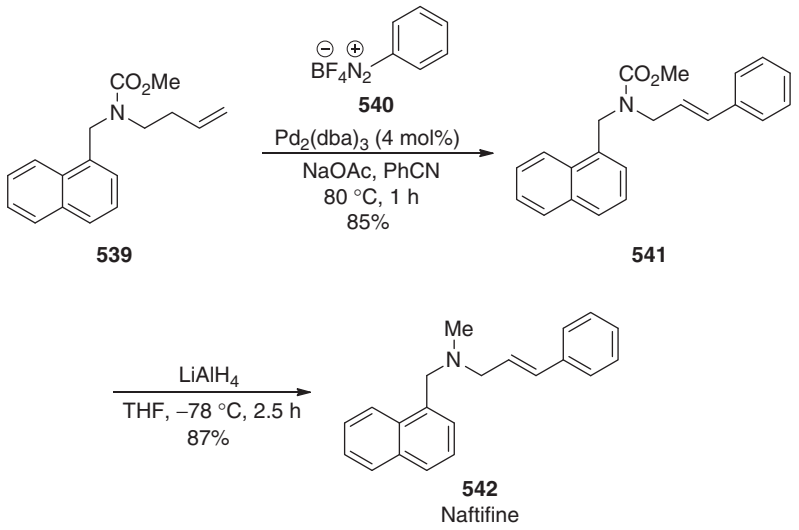
Scheme 60

The reaction proceeds through an intermolecular reaction between the allylic alcohol and aromatic iodide in the presence of $Pd(OAc)_2$ and Et_3N in CH_3CN in a nonphase transfer reaction. The regioselectively formed product tautomerizes to give the ketone **537** in 83% yield. This reaction is used on an industrial scale to create the framework of this pharmaceutical compound in an efficacious manner.

4.14.11.2 Chelation Control – Naftifine and Abamines

The chelation-controlled Heck reaction has recently been applied to the synthesis of the bioactive compounds Naftifine (**542**) and Abamines.[309] The amide carbonyl of the allylamine substrate **539** is proposed to coordinate to Pd, controlling the regioselectivity of the reaction.

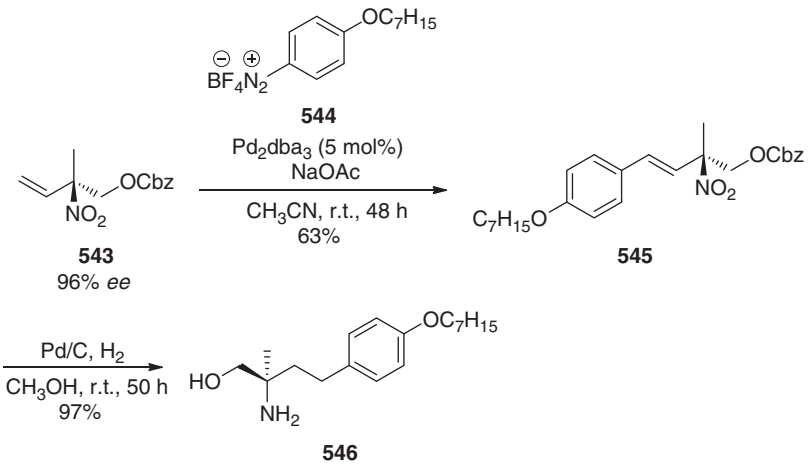
This simple and mild Heck arylation of allylamine derivatives by Correia employs arenediazonium salts, giving high overall yields and concise routes toward these biologically active compounds and their analogs (Scheme 61).



Scheme 61

4.14.11.3 Heck Reaction on Allylic Nitro Compounds – FTY720

Kamimura recently developed a synthesis of derivatives of FTY720 (2*R*-amino[2-(4-octylphenyl)ethyl]-1,3-propanediol) (**546**), a potent immunosuppressive used to treat multiple sclerosis and other autoimmune diseases.[310] Using the Heck–Matsuda reaction as a key step, FTY720 analogs were synthesized in three steps, one of which is shown in Scheme 62. The allylic nitro compound **543** (96% *ee*) undergoes the Heck–Matsuda reaction with *p*-heptyloxylphenyldiazonium salt in the presence of $Pd_2(dba)_3$ to give the desired product **545** in 63% yield with retention of configuration at the stereogenic center. The active compound is generated by group and double bond reduction.

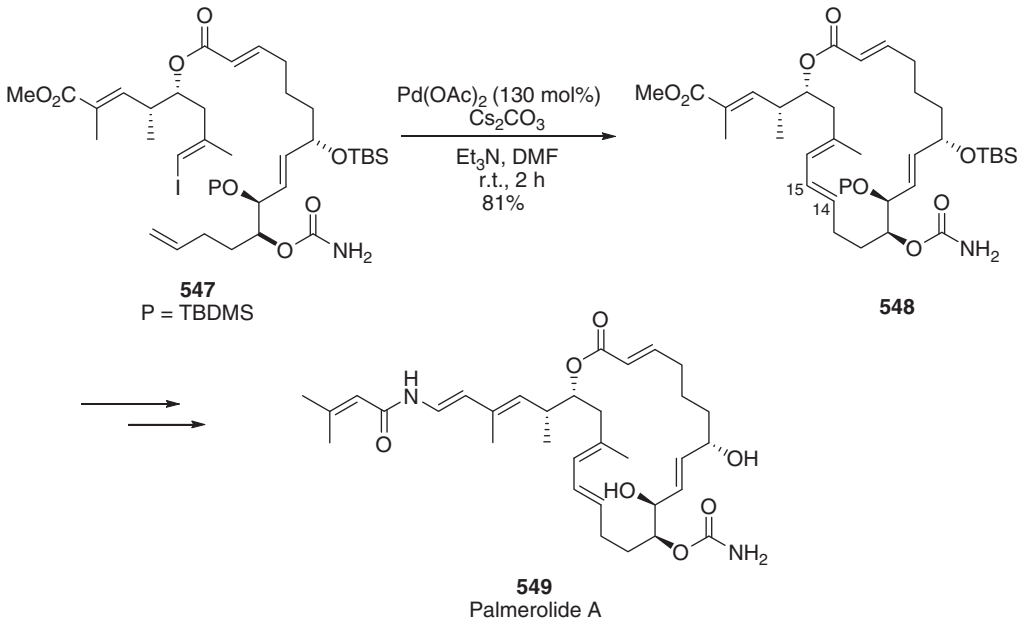


Scheme 62

4.14.11.4 Intramolecular Heck Reaction – Palmerolide A and Dichroanal B

Palmerolide A **549** was isolated from the Antarctic marine tunicate *Synoicum adareanum* by Baker in 2006.[311] This macrolide has a unique cytotoxicity profile as it acts as a potent inhibitor of vacuolar V-ATPase. Testing on melanoma cell line UACC-62 has shown

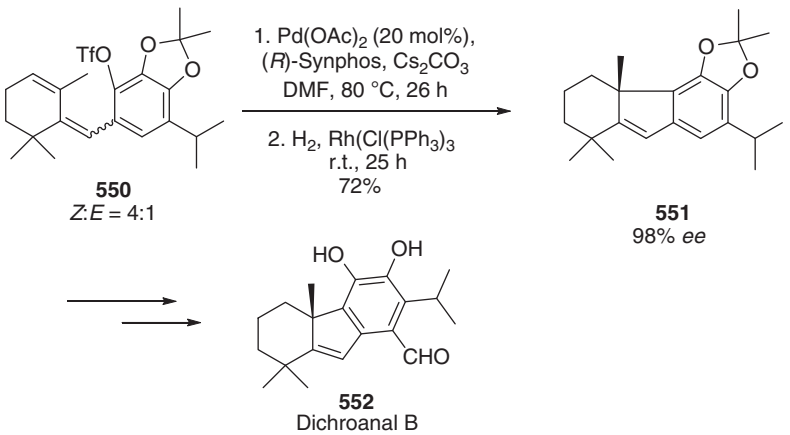
the molecule to be quite potent (LC_{50}=18 nM). Maier has developed a concise formal synthesis of the macrolactone using the Heck reaction to prepare an *E,E*-diene containing macrocycle, an advanced intermediate in the Nicolaou/Chen synthesis of palmerolide A.[312] Using the Heck cyclization an isomerically pure lactone was synthesized at room temperature using $Pd(OAc)_2$, $CsCO_3$, and Et_3N in DMF (Scheme 63). Originally an intramolecular Stille coupling reaction was attempted to form the C14–C15 double bond but this generated an *E/Z* mixture of products.



Scheme 63

Node synthesized *abeo*-abientane-type diterpenoids, including dichroanal B **552**, using an intramolecular Heck reaction to give higher overall yields with a shorter synthetic route than previous approaches to these compounds.[313] These compounds were of interest as similar diterpene-containing *abeo*-arbietanes have shown interesting biological activity, for example standishinal has potent anticancer activity against postmenopausal breast cancer.[314]

After attempting a number of different reaction conditions for the intramolecular Heck reaction it was found that the reaction was highly temperature dependent. Using (*R*)-Synphos and conducting the reaction over 26 h at 80 °C gave a yield of 72% and a 98% *ee* after hydrogenation (Scheme 64). The use of the Heck reaction in this synthetic strategy generated the product in 50% overall yield in 10 steps, which is a higher yield and a shorter sequence than previously reported.[313a,b]



Scheme 64

Pd has a high functional group tolerance and an excellent capacity for carbon–carbon bond formation. The value of the Heck reaction can be seen in the breadth of the syntheses it has been applied to. These include: Danishefsky's taxol synthesis,[114,315]

Overman's quadrigemine C synthesis,[316] Tietze's synthesis of estrone,[317] Trost's synthesis of 1α-hydroxyvitamin D (calcidiol),[318] and Corey's synthesis of okaramine N,[319] to name but a few. These examples and those shown in detail above, illustrate the importance of the Heck reaction as a carbon–carbon bond forming step in total synthesis.

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4.15 Carbometalation and Heterometalation Reactions of Alkenes, Alkynes, and Allenes

A Ding and H Guo, Fudan University, Shanghai, P. R. China

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Glossary

Aminocupration The addition reaction of a nitrogen–copper bond to a carbon–carbon unsaturated bond.

Aminolithiation The addition reaction of a nitrogen–lithium bond to a carbon–carbon unsaturated bond.

Arene dianions An arene having two negative charges.

Carbomanganation The addition reaction of a carbon–manganese bond to a carbon–carbon unsaturated bond.

Carbostannylation The addition reaction of a carbon–stannum bond to a carbon–carbon unsaturated bond.

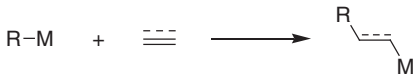
Oxymercuration The addition reaction of a oxygen–mercury bond to a carbon–carbon unsaturated bond.

Thioboration The addition reaction of a sulfur–boron bond to a carbon–carbon unsaturated bond.

4.15.1 Carbometalation of Alkenes, Alkynes, and Allenes

4.15.1.1 Introduction

Carbometalation reaction was discovered by Ziegler and Bähr,[1] which has been widely applied in organic syntheses. With this methodology, a new carbon–carbon bond and a new carbon–metal bond can be constructed simultaneously (equation 1), and the resultant organometallic compound can be further used for subsequent transformations. The carbometalation reactions may result in a mixture of regio- and/or stereoisomers. To draw a conclusion, simply stating the difference of the selectivities between main group metals and transition metals is not easy, since this depends on not only the nature of the reactants, but also on the corresponding reaction conditions. The decisive factors for this matter will be discussed in their respective sections. As a continuation of Volume 1, only the recent new advents and classic developments after 1990 in this field are reviewed. In this part, the carbolithiation, carbomagnesiation, carbozincation, carboboration, carboalumination, carbocupration, carbostannylation, and carbomanganation of alkenes, alkynes, and allenes are introduced in detail. The mechanism and potential applications are also presented.



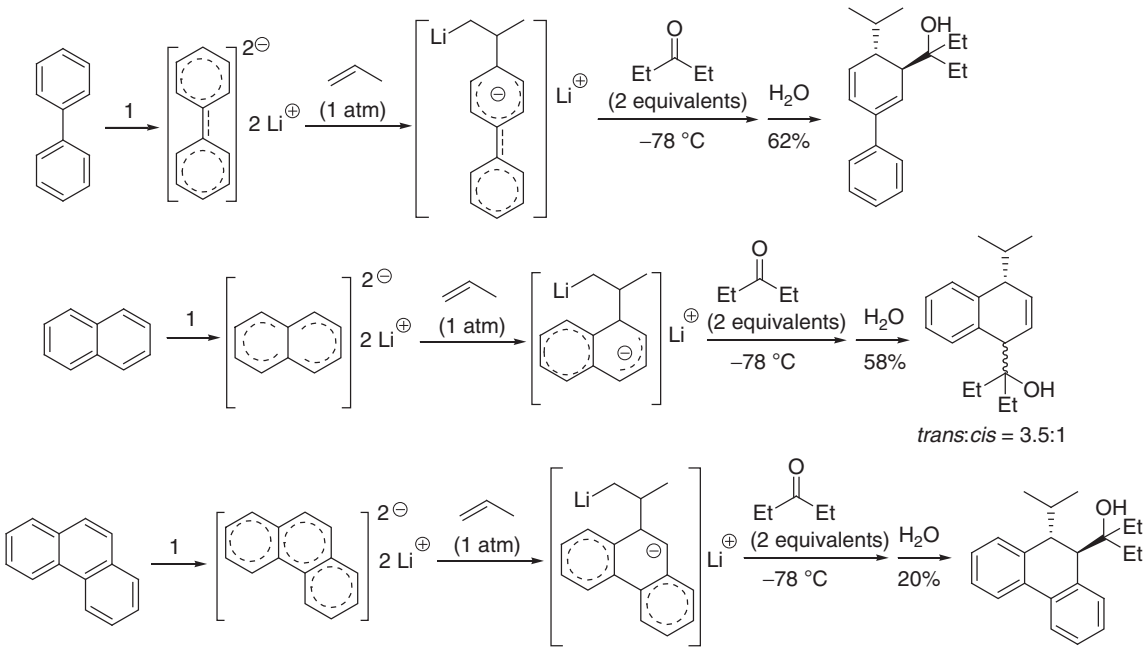
(1)

4.15.1.2 The Carbolithiation Reaction

4.15.1.2.1 The Carbolithiation of Alkenes

4.15.1.2.1.1 Intermolecular reactions

Some arene dianions generated from the reactions of lithium powder with high reductive aromatic hydrocarbons, such as biphenyl, naphthalene, and phenanthrene, react with terminal alkenes in a highly regioselective manner. Only the partially dearomatized arylated primary alkyllithium compounds are formed. These carbometalated species can be further transformed by *in situ* electrophilic capture and hydrolysis work up (Scheme 1).[2] For biphenyl, the addition with pentan-3-one occurs at C^3 position, affording the *trans*-3,4-dihydrobiphenyl derivative in moderate yield. For naphthalene, a mixture of *trans*-preferred

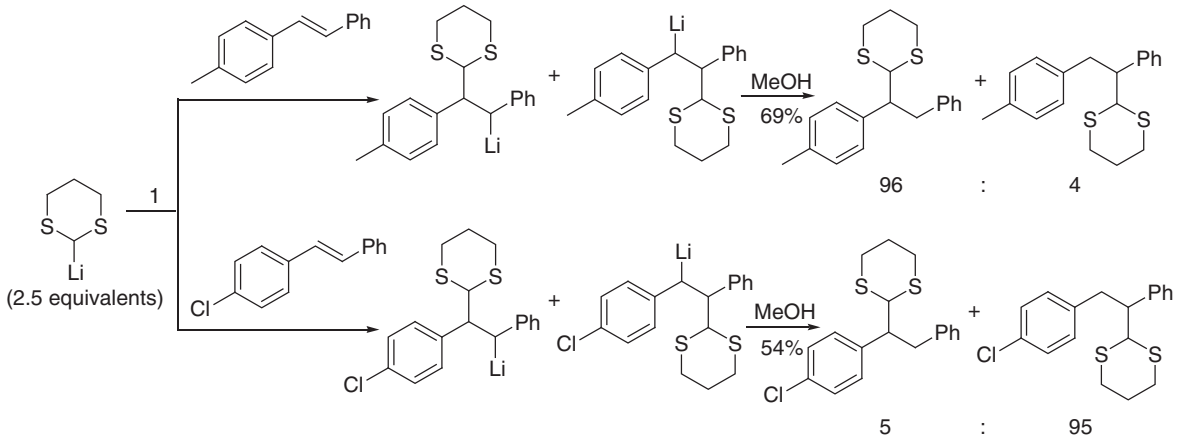


1. Li (4 equivalents), THF, 25 °C

Scheme 1

1,4-dihydronaphthalene species is yielded. For phenanthrene, this addition does not proceed in a synthetically useful way, only a very low yield of *trans*-9,10-dihydrophenanthrene derivative is produced.

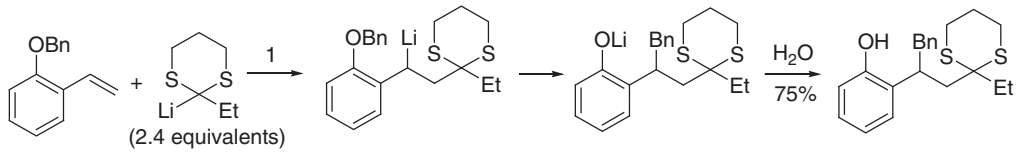
In the (1,3-dithian-2-yl)lithiation of stilbene derivatives, high regioselectivities can be achieved even when there is only a slight electronic difference between the two phenyl rings (Scheme 2),[3] since the alkyl group is regiospecifically installed to the electron-deficient terminus of the carbon–carbon double bond.



1. HPMA (1–3 equivalents), Et_2O, –50 °C to r.t., 3 h

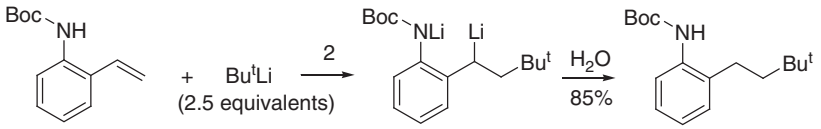
Scheme 2

The addition of alkyllithium reagents to arylstyrenes, like *ortho*-alkoxystyrenes (equation 2),[3] *ortho*-(*N*-Boc)-styrenes (equation 3),[4] and 2-(*N*-Boc)-3-vinylpyridines (equation 4),[5] affords only the benzylic lithium species in high regioselectivity due to the benzylic effect.



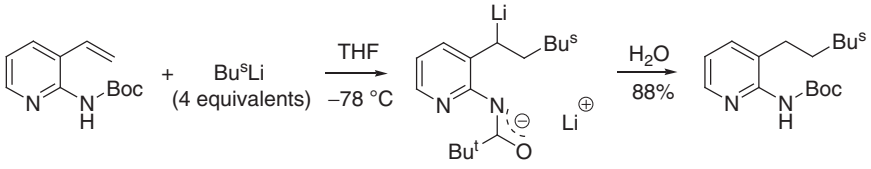
(2)

1. HMPA (6 equivalents), Et_2O, –50 °C to r.t., 2 h



(3)

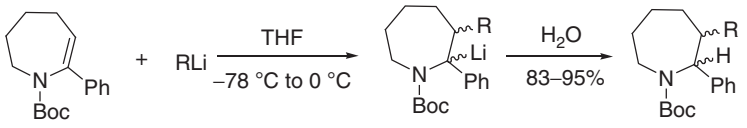
2. TMEDA (2 equivalents), Et_2O, –78 °C, 1.5 h



(4)

The addition to cyclic styrene derivative **1** with alkyl- or phenyllithium reagents occurs readily in tetrahydrofuran (THF) under low temperature, showing the same benzylic selectivity (Scheme 3).[6] Primary and secondary alkyllithium reagents are more reactive than tertiary alkyllithium.

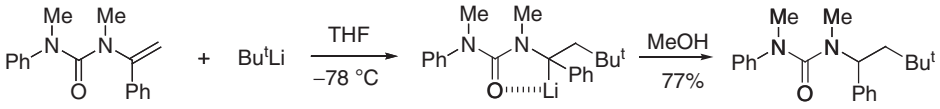
For *β*-carbonyl styrenes, like the (1-phenylvinyl)urea derivative **2**, the corresponding carbolithiation undergoes a similar reaction to yield benzylic organolithium **3** as the only product (Scheme 4).[7] However, in such a case, the coordination effect of the *β*-carbonyl group may be also an important reason for the regioselectivity.



1

R = Me, Bu^n, Bu^s, Bu^t, or Ph

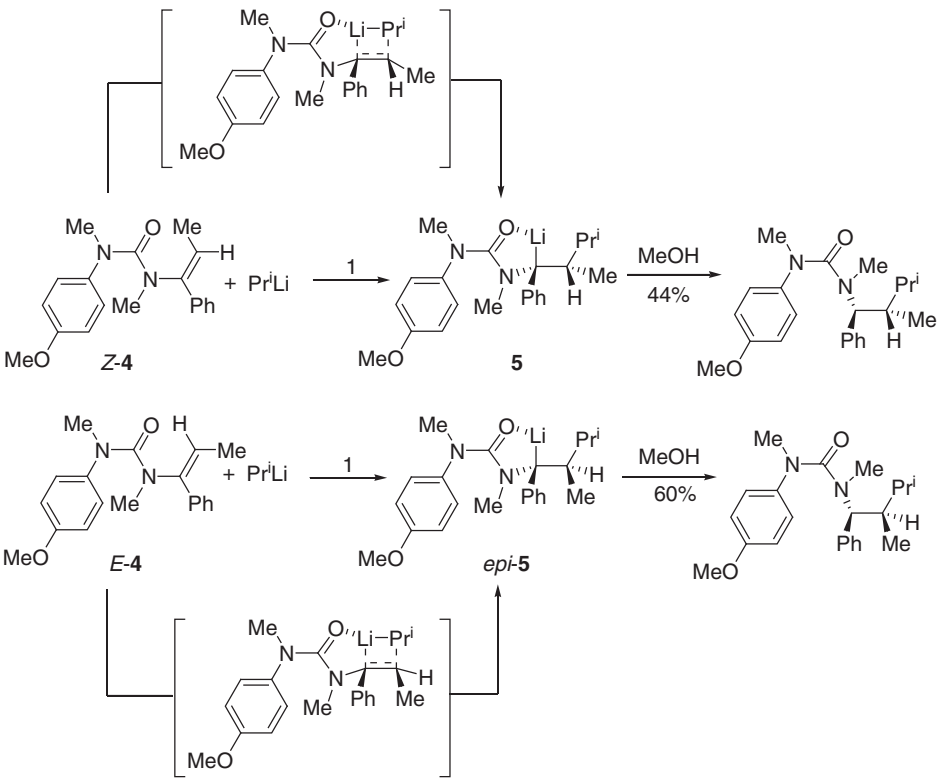
Scheme 3



2 **3**

Scheme 4

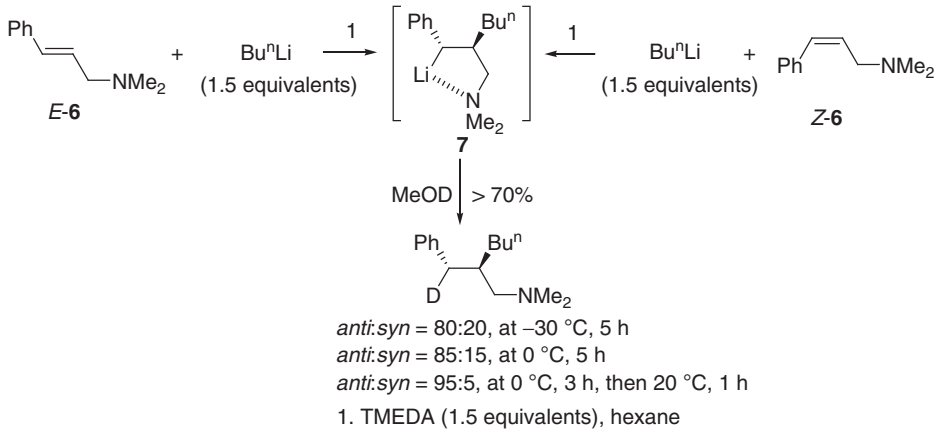
Furthermore, the addition of *Z*- or *E*-(1-phenylprop-1-enyl)urea derivatives **4** with Pr^iLi gives epimeric products **5**, which indicates that the *cis*-carbolithiation proceeds selectively via the configurationally stable transition state influenced by the adjacent carbonyl group (Scheme 5).[7]



1. Toluene, –40 °C, 1 h

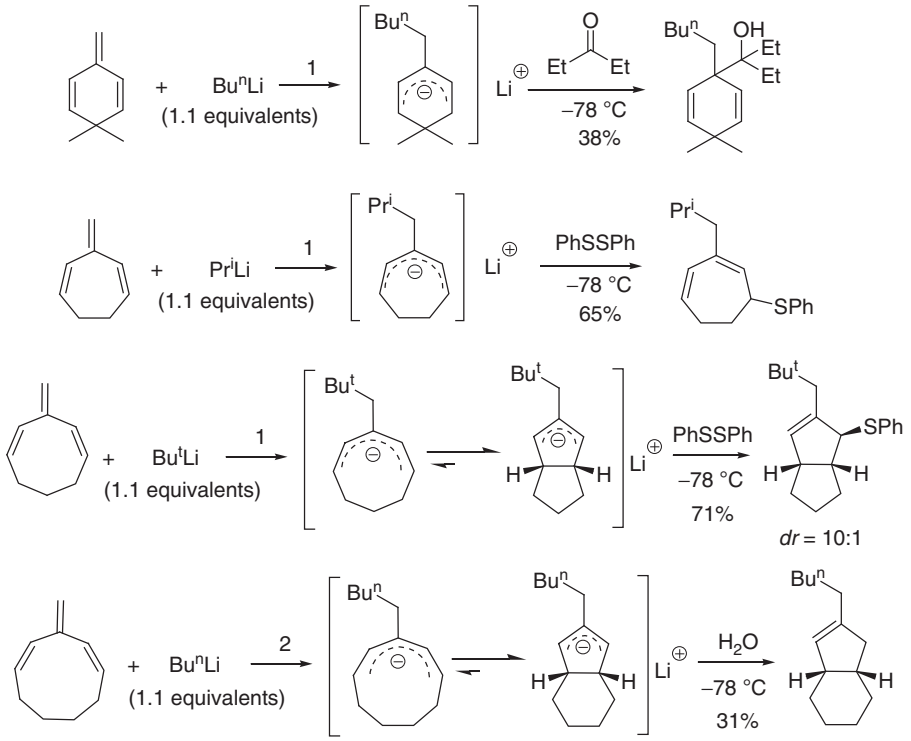
Scheme 5

The carbolithiation of cinnamylamine **6** with Bu^nLi in the presence of tetramethylethylenediamine (TMEDA) produces organolithium **7** under controlled conditions (Scheme 6).[8] The *anti*-isomer is formed as the major product, starting from either *E*- or *Z*-cinnamylamine. A better diastereoselectivity is obtained at higher reaction temperatures after complete conversion, which indicates that there is a thermodynamically controlled equilibration of the *anti*- and *syn*-organolithium species. It is quite synthetically useful, since the generated single isomer reacts stereoselectively with electrophiles to give diastereomerically pure products.



Scheme 6

The additions to six- through nine-membered 3-methylene-1,4-cycloalkadienes give the corresponding cyclic conjugated pentadienyl carbanions (Scheme 7).[9] Primary, secondary, and tertiary alkyllithium reagents may all be employed. The ring size plays a crucial role in the reactivity of the resulting anions. For six- or seven-membered ring systems, functionalized cyclohexadiene or cycloheptadiene derivatives can be achieved by direct treatment with electrophiles. For eight- or nine-membered ring systems, the formed carbanions undergo highly stereoselective disrotatory electrocyclization to form *cis*-bicyclo[3.3.0]octenyl or *cis*-bicyclo [4.3.0]nonenyllithium species as the major product, which can be further transformed with a variety of electrophiles.

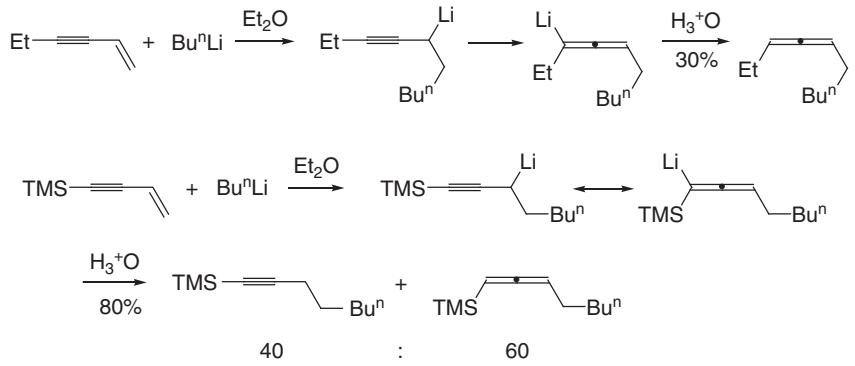


1. Et_2O, –78 °C to r.t.; 2. TMEDA/hexane, –78 °C to 120 °C, 1 h

Scheme 7

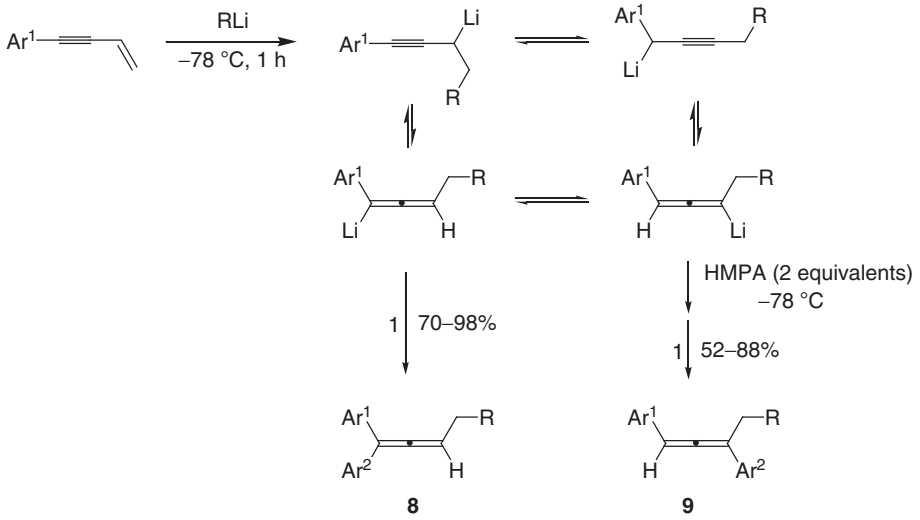
The carbolithiation of conjugated enynes normally yields propargylic lithium intermediates which may easily isomerize into allenic lithium species. The addition of nonfunctionalized conjugated enynes is of limited preparative interest, since the generated mixture of propargylic and allenyllic lithium is only formed in a very low yield or quite poor selectivity (Scheme 8).[10]

While for 4-aryl-3-butyn-1-ene derivatives, their carbolithiation gives much better results. Ma developed a convenient protocol to synthesize 1,1-diarylallenes **8** or 1,3-diarylallenes **9** via a process of carbolithiation, isomerization, transmetallation,



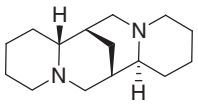
Scheme 8

and Pd(0)-catalyzed coupling reaction. The key step, 1,3-lithium shift between propargylic and allenyllic species, is well controlled by applying or not applying hexamethylphosphoric triamide (HMPA), affording sole **8** or **9** with excellent selectivities in good to excellent yields. This reaction is quite general for different 4-aryl-3-butyn-1-enes and aryl iodides. Primary, secondary, and tertiary alkyllithium reagents can all be used (Scheme 9).[11]



Scheme 9

Since the first asymmetric carbolithiation reaction of cinnamyl derivatives developed by Marek and coworkers[12] the easily available natural product (−)-sparteine (Scheme 10) became an efficient auxiliary ligand for the enantioselective carbolithiation reactions.

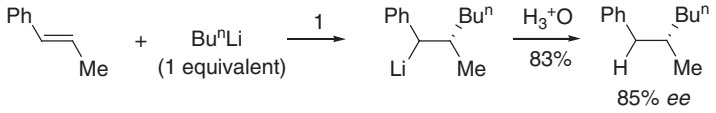


(−)-Sparteine

Scheme 10

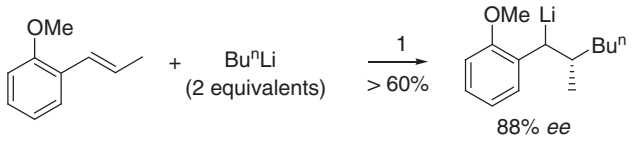
The (−)-sparteine-mediated enantioselective intermolecular carbolithiation of nonfunctionalized styrenes with primary alkyllithium occurs at low temperature, affording only the benzylic lithium species in good *ee* (Scheme 11).[13] *E*-styrene derivatives

give much higher yields as well as *ee* values than *Z*-isomers accordingly. The reactions of *ortho*-heteroatomsubstituted-*β*-methylstyrenes lead to similar results (Schemes 12 and 13).[14]



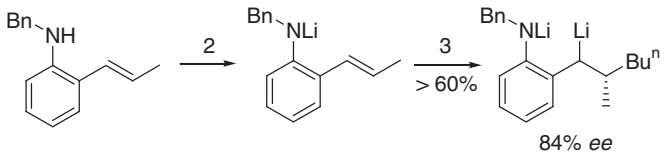
1. (–)-Sparteine (1 equivalent), hexane, –15 °C

Scheme 11



1. (–)-Sparteine (3 equivalents), cumene or Et_2O, –40 °C

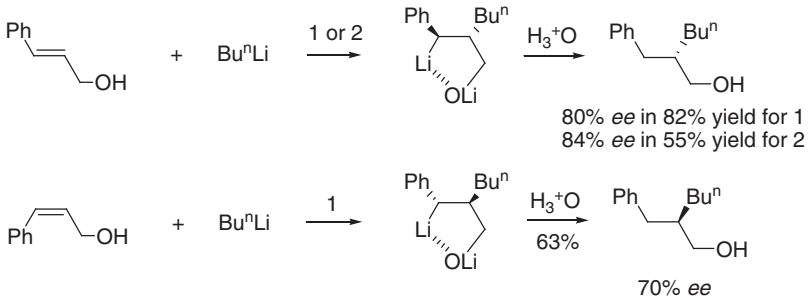
Scheme 12



2. Cumene, PhLi (1 equivalent), r.t.; 3. (–)-Sparteine (3 equivalents), BunLi (1 equivalent), –15 °C

Scheme 13

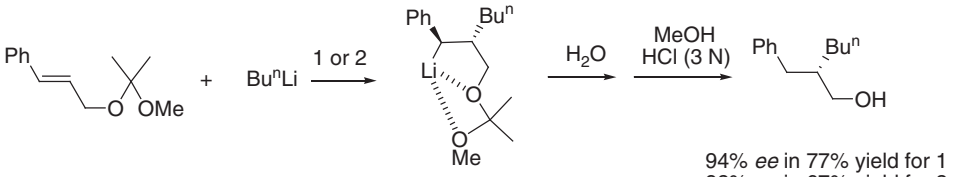
In the presence of 1 equivalent of (−)-sparteine, the reaction of cinnamyl alcohols results in the formation of chiral benzylic organolithium, which is thermodynamically favored. In donor solvents, this reaction gives poor enantioselectivities. Although in cumene or hexane, a good *ee* reaching up to 80% can be achieved. Both *E*- and *Z*-cinnamyl alcohols are suitable substrates in this reaction, but the *Z*-isomer results in a lower *ee* value in poorer yield under the same reaction conditions (Scheme 14).[12] Without (−)-sparteine, this reaction does not take place at 0 °C, which implicates the possibility of this reaction in a catalytic manner. In fact, a catalytic amount of (−)-sparteine (5 mol%) in hexane at 0 °C leads to a slightly higher *ee*, although the yield is much lower (Scheme 14).[12]



1. (–)-Sparteine (1 equivalent), cumene, 0 °C; 2. (–)-Sparteine (5 mol%), hexane, 0 °C

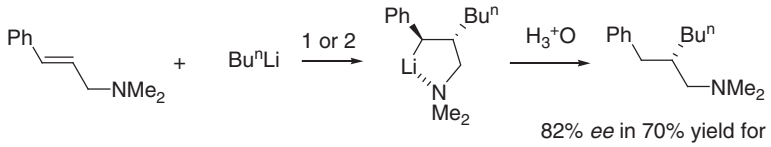
Scheme 14

Similarly, the (−)-sparteine-mediated or catalyzed additions of alkyllithium to cinnamyl acetal (Scheme 15)[15] or (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine (Scheme 16)[12] at low temperature yield the corresponding chiral benzylic organolithium with high regio- and enantioselectivities.



1. (–)-Sparteine (1 equivalent), hexane, –50 °C; 2. (–)-Sparteine (10 mol%), hexane, –50 °C

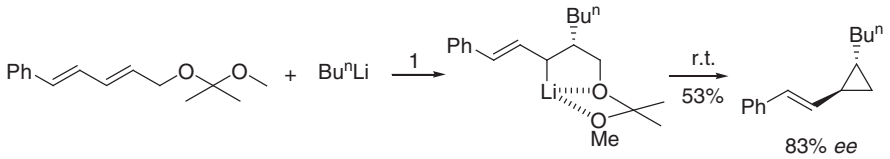
Scheme 15



1. (–)-Sparteine (1 equivalent), cumene, 0 °C; 2. (–)-Sparteine (5 mol%), hexane, 0 °C

Scheme 16

(–)-Sparteine can also catalyze the addition of *n*-alkyllithium to 5-alkoxypenta-1,3-diene derivatives, affording the allylic organolithium species which can be converted into cyclopropanes with good enantioselectivities (Scheme 17).[16] The alkyl group is regioselectively introduced close to the binding group.



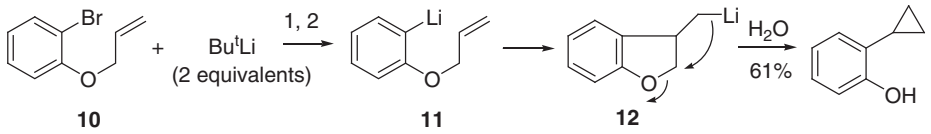
1. Hexane, (–)-Sparteine (10 mol%), –10 °C

Scheme 17

4.15.1.2.1.2 Intramolecular reactions

The construction of ring systems by intramolecular carbolithiation is a useful synthetic transformation. This methodology has been extended to the preparation of not only carbocycles, but also heterocycles. Lithium–halogen exchange is the most used method to start such reactions.

The treatment of allyl 2-bromophenyl ether **10** with 2 equivalents of Bu^{t}Li forms the corresponding aryllithium intermediate **11** which undergoes intramolecular cyclization in the presence of TMEDA to produce the lithiated *trans*-2,3-dihydrobenzofuran derivative **12** (Scheme 18).[17]

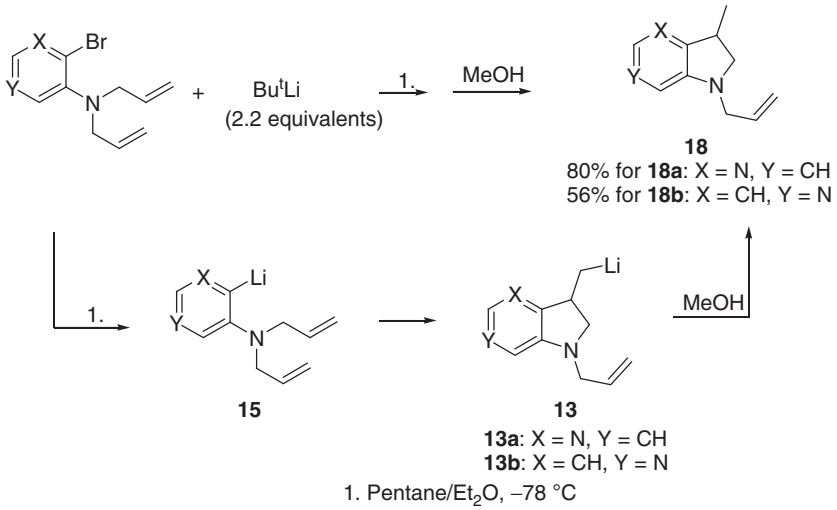


1. Et_2O, –78 °C; 2. TMEDA (2.2 equivalents), –78 °C to 0 °C

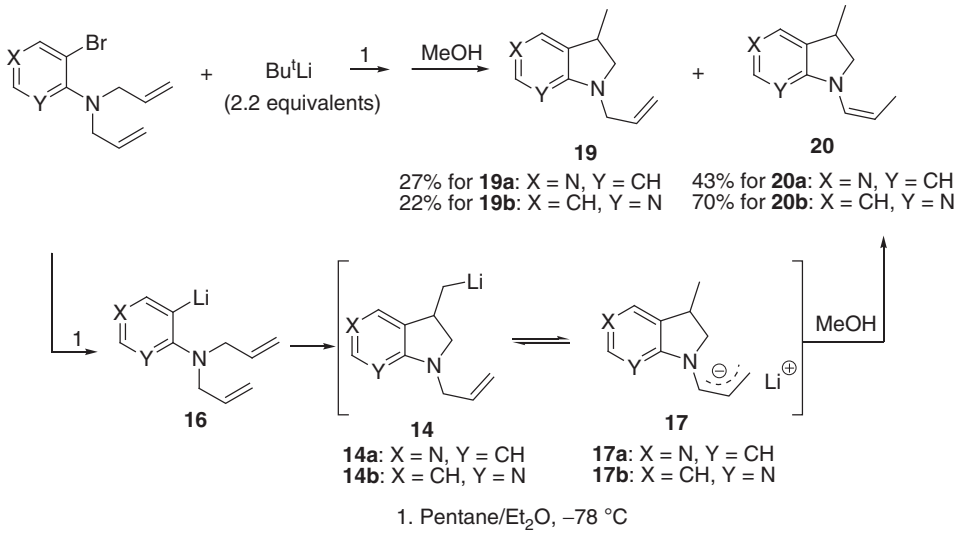
Scheme 18

Similarly, four isomeric azaindoline lithium **13** or **14** can be prepared by intramolecular 5-*exo* cyclization of aryllithium **15** or **16** (Schemes 19 and 20).[18] The alkyllithium intermediates **14** will further isomerize to π-allyllithium species **17** smoothly via intramolecular Li–H exchange.

Vinyllithium **21** undergo 5-*exo* and/or 6-*endo* intramolecular carbolithiation in the presence of TMEDA. The regioselectivity highly depends on the electron density of the nitrogen atom. When electron-rich nitrogen reactants like benzyl amine **22a** is used, the insertion of the alkene moiety into the C–Li bond occurs absolutely in a regiospecific 5-*exo* fashion, merely affording alkyllithium **23**. However, when phenyl amine **22b** which has less electron density on the nitrogen atom is applied, the 6-*endo*



Scheme 19



Scheme 20

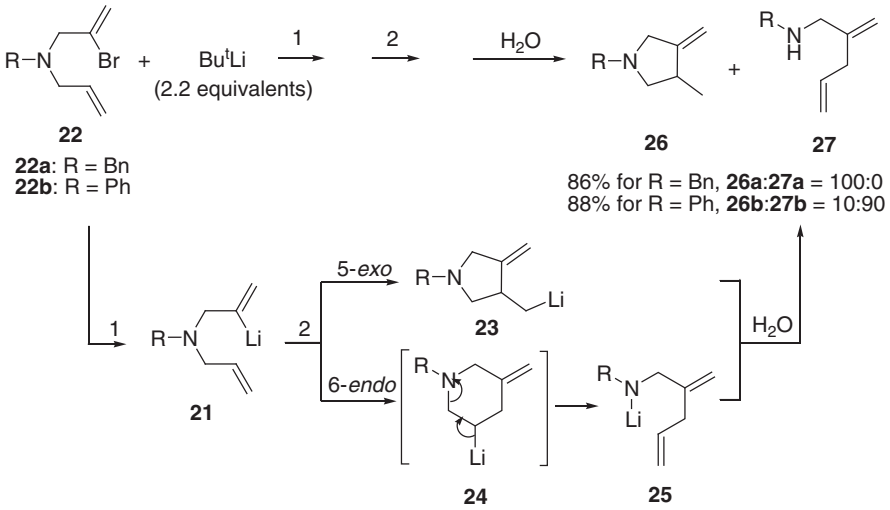
cyclization is favored to produce the organolithium intermediate **24**. The subsequent β-elimination forms lithium amide **25** as the major product (Scheme 21).[19]

Bis(2-lithioallyl)amine **28** affords dilithiated intermediate **29** by the addition of one carbon–carbon double bond. The subsequent lithium transfer generates dilithiated dihydropyrrole species **30** (Scheme 22).[20]

The reaction of organolithium **31** forms a similar dilithiated intermediate **32** which yields 3-lithiomethylindole derivative **33** by the elimination of lithium hydride (Scheme 23).[20]

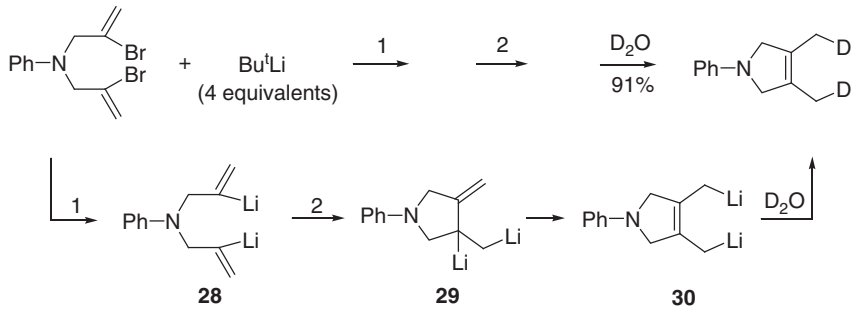
The chiral α-amino-organolithium **34** afforded by transmetallation of the corresponding organostannane **35** undergoes intramolecular carbolithiation to give the cyclized organolithium intermediate **36** without any loss of the optical purity. After quenching with methanol, a single diastereoisomer, (+)-pseudoheliotridane **37**, is produced in a high yield (Scheme 24).[21] The chemistry of (*S*)-1-(pent-4-enyl)-2-(tributylstannyl)pyrrolidine **38** is not the same (Scheme 25).[21] The desired enantiomerically enriched organolithium intermediate **39** can be easily generated by the tin–lithium exchange, but cyclizes into a mixture of lithiated indolizidine diastereoisomers **40**. The diastereoselectivities can be easily controlled under optimized conditions. In the absence of TMEDA, a high diastereoselectivity of 95:5 with the *trans*-isomer formed as the major product is observed. Although in the presence of TMEDA, a reversal of the diastereoselectivity ratio is obtained, in which the *cis*-isomer turns to be the major one. However, the chirality transfer is not efficient, since epimerization of **39** is faster than cyclization. In some cases, only racemic products are formed.

(−)-Sparteine is also widely applied in intramolecular asymmetric carbolithiations. Although an excess amount is always required in all reported cases, the achieved enantioselectivity is still not high in most examples.



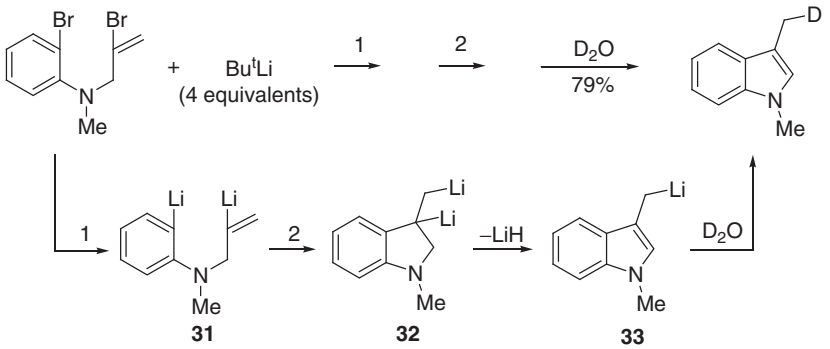
1. Et_2O, –78 °C; 2. TMEDA (2.2 equivalents), –78 °C to 0 °C

Scheme 21



1. Et_2O, –78 °C; 2. TMEDA (4 equivalents), –78 °C to 20 °C

Scheme 22

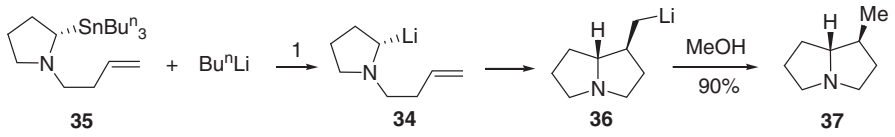


1. Et_2O, –78 °C; 2. TMEDA (4 equivalents), –78 °C to r.t.

Scheme 23

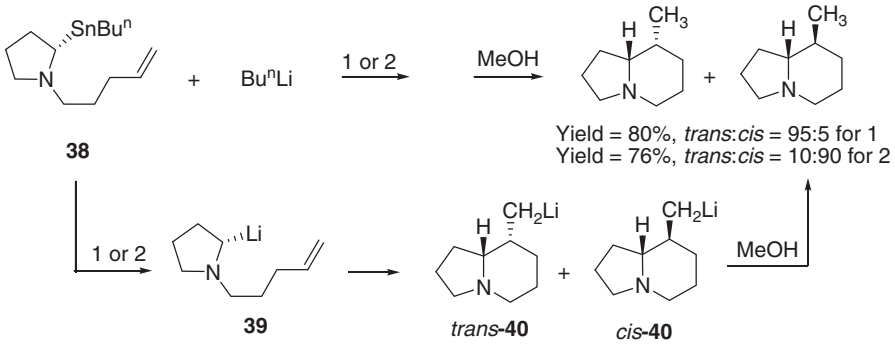
The intramolecular carbolithiation of simple substrates like hepta-1,6-dien-2-yllithium **41**, derived from the bromo–lithium exchange of 2-bromo-1,6-heptadiene with 2.2 equivalents of Bu^{t}Li at −78 °C, affords (*S*)-((2-methylenecyclopentyl)methyl) lithium **42** with low *ee* value (Scheme 26).[22]

Aryllithium **43** forms chiral (1-indanyl)methyllithium **44** via the (−)-sparteine-mediated asymmetric intramolecular carbolithiation process which gives (*S*)-1-methyl-2,3-dihydro-1*H*-indene with an *ee* value of 42% after protonation. Although for the



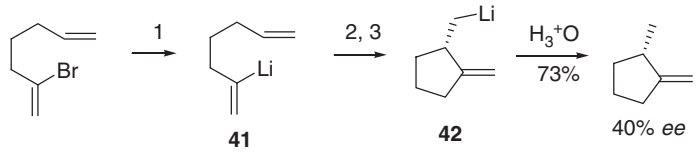
1. Hexane/Et_2O = 10:1, r.t., 2 h

Scheme 24



1. Hexane/Et_2O = 4:1, r.t., 6 h; 2. Hexane/Et_2O/TMEDA = 4:1:1, r.t., 6 h

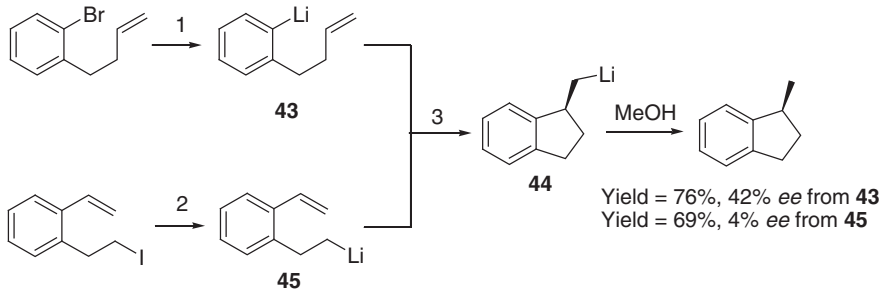
Scheme 25



1. Bu^{t}Li (2.2 equivalents), *n*-C_5H_{12}/Et_2O = 9:1, –78 °C; 2. (–)-Sparteine (2.2 equivalents);
3. 0 °C, 2.5 h

Scheme 26

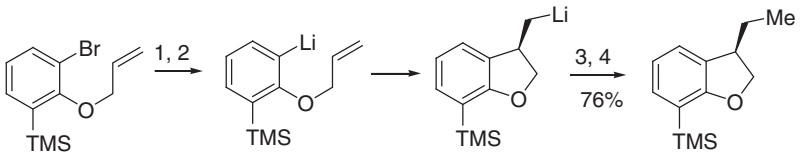
reaction of alkyllithium **45**, the same organolithium product **44** is formed with a very low enantioselectivity under identical conditions (Scheme 27).[22] In both cases, no 6-*endo* cyclization occurs.



1. Bu^{t}Li (2.2 equivalents), *n*-C_5H_{12}/Et_2O, –78 °C
2. Bu^{t}Li (1.8 equivalents), *n*-C_5H_{12}/Et_2O, –78 °C
3. (–)-Sparteine (2.2 equivalents)

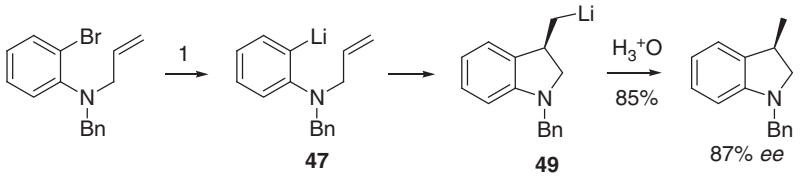
Scheme 27

Similarly, the cyclization of aryllithium **46** or **47** gives alkyllithium intermediates **48** or **49** which can react with a variety of electrophiles to produce a series of 2,3-dihydrobenzofuran or indoline derivatives in good yields with good *ee* (Schemes 28 and 29).[17b,23]



1. Bu^tLi (2 equivalents), Pr^i_2O, –78 °C; 2. (–)-Sparteine (2.2 equivalents), –78 °C to –50 °C
3. Me_2SO_4 (1.1 equivalents), –78 °C to 20 °C; 4. H_2O

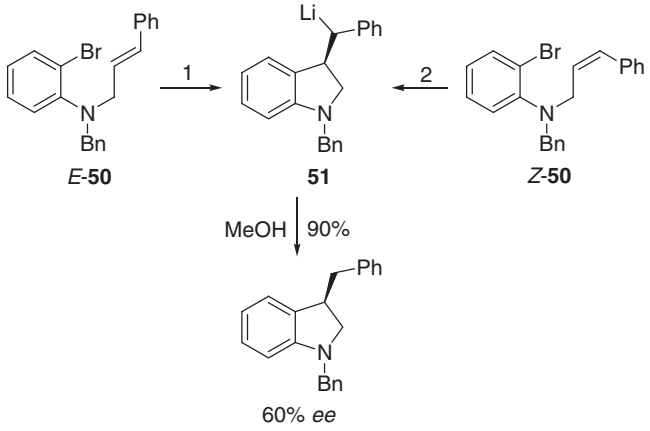
Scheme 28



1. Bu^tLi (2.2 equivalents), (–)-sparteine (1.5 equivalents), toluene, –90 °C

Scheme 29

For the reactions of 1,2-disubstituted alkenes **50**, the bromo–lithium exchange can take place at −78 °C, but higher temperature (−50 °C) is required for the following cyclization. Notably, no significant difference is observed on the stereochemical outcome as well as the yield of the hydrolyzed products, which implicates that the same organolithium intermediate **51** is always formed from *E*- or *Z*-alkenes (Scheme 30).[23]



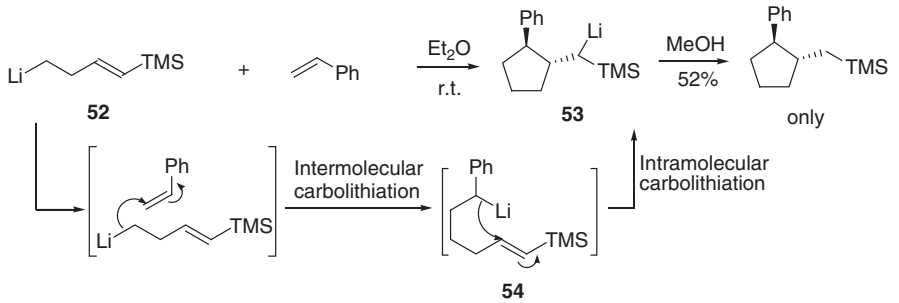
2. Bu^tLi (2.2 equivalents), (–)-sparteine (1.5 equivalents), toluene, –78 °C to –50 °C

Scheme 30

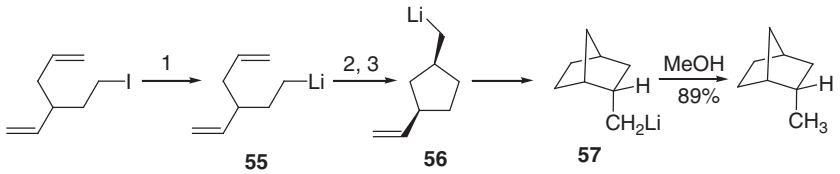
4.15.1.2.1.3 Cascade reactions

The reaction of (*E*)-(4-trimethylsilylbut-3-enyl)lithium **52** with styrene affords organolithium **53** via a tandem inter- and intramolecular carbolithiation process. The intermolecular addition to styrene highly regioselectively forms the benzylic lithium intermediate **54** which undergoes the subsequent intramolecular carbolithiation to generate the cyclic organolithium species **53**. The whole process is highly regio- and stereoselective and only the *trans*-five-membered cyclic product is formed in this reaction (Scheme 31).[24]

The (3-vinylhex-5-enyl)lithium **55**, generated by the iodide–lithium exchange of 3-(2-iodoethyl)-1,5-hexadiene with Bu^tLi, proceeds in a highly regio- and stereoselective intramolecular cyclization in the presence of TMEDA, affording ((*cis*-3-vinylcyclopentyl)methyl)lithium intermediate **56** which subsequently forms ((*endo*-2-bicyclo[2.2.1]heptyl)methyl)lithium species **57** after the second intramolecular cyclization (Scheme 32).[25]



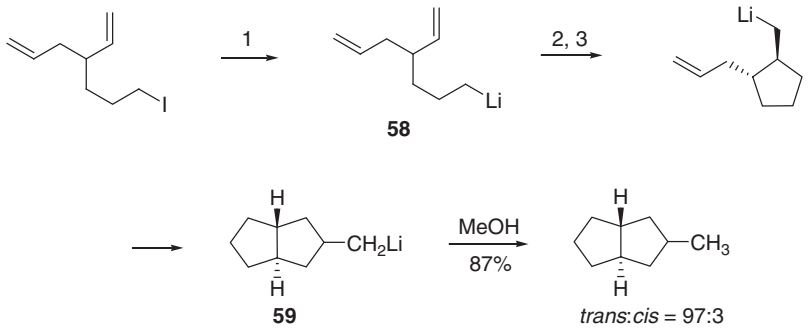
Scheme 31



1. Bu^{t}Li (2.2 equivalents), pentane/diethyl ether = 3:2, –78 °C; 2. TMEDA (2.2 equivalents), –78 °C; 3. 0 °C

Scheme 32

A similar reaction of (4-vinylhept-6-enyl)lithium **58** yields *trans*-bicyclo[3.3.0]octane lithium derivative **59** as the major product via the same two-step cyclization process (Scheme 33).[25]



1. Bu^{t}Li (2.2 equivalents), pentane/diethyl ether = 9:1, –78 °C
2. TMEDA (2.2 equivalents), –78 °C; 3. 0 °C

Scheme 33

4.15.1.2.2 The Carbolithiation of Alkynes

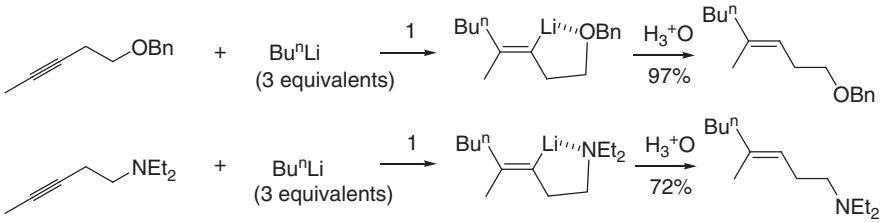
4.15.1.2.2.1 Intermolecular reactions

The intermolecular carbolithiation of alkynes is rarely used in synthetic approaches, because the reactions of nonfunctionalized alkynes give rather poor regio- and stereoselectivies and the formed vinyllithium intermediates isomerize easily. When there is a heteroatom at the proper position, the selectivities can be well controlled. In 2001, Hosomi et al. reported the Fe-catalyzed highly regio- and stereoselective carbolithiation of alkynes. Both benzylpent-3-yn-1-ether and *N*,*N*-diethylpent-3-yn-1-amine lead to the formation of a single vinyllithium product (Scheme 34).[26]

4.15.1.2.2.2 Intramolecular reactions

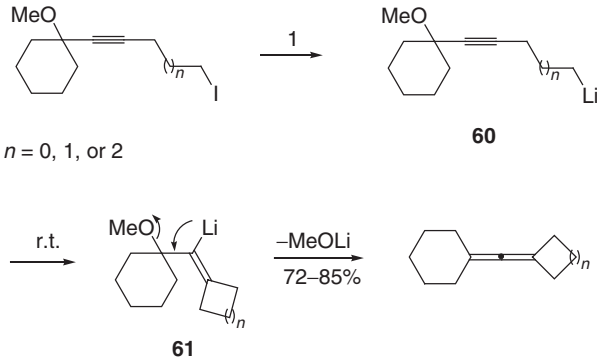
Achievements in the field of intramolecular carbolithiation of alkynes are not numerous. And *syn*-addition via an *exo*-process is always preferred affording a smaller ring system with a lithiated exocyclic double bond.

Acetylenic alkyllithium **60** undergo intramolecular carbolithiation to yield four- through six-membered cyclic vinylic lithium **61** which give allene derivatives by the elimination of MeOLi (Scheme 35).[27]



1. $Fe(acac)_3$ (10 mol%), toluene, –20 °C

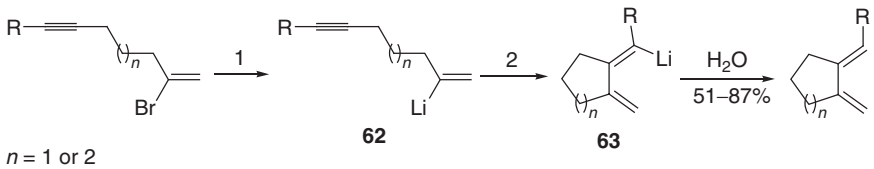
Scheme 34



1. Bu^tLi (2 equivalents), n-C_5H_{12}/Et_2O = 3:2, –78 °C

Scheme 35

The cyclization of acetylenic vinyllithium **62** proceeds regioselectively via an *exo*-process and stereoselectively via the *syn*-addition, affording conjugated bisexocyclic 1,3-dienyllithium **63** as the single product (**Scheme 36**).[28]



n = 1 or 2
R = alkyl, silyl, or aryl

1. Bu^tLi (2 equivalents), n-C_5H_{12}/Et_2O, –100 °C to –78 °C; 2. 0 °C to 40 °C

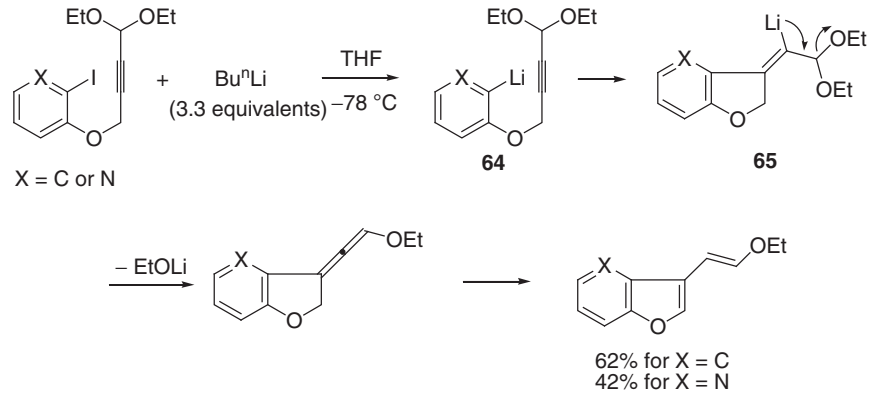
Scheme 36

For the reaction of aryllithium intermediates **64**, bicyclic vinyllithium species **65** are produced which finally give (*E*)-3-(2-ethoxyvinyl)benzofuran or (*E*)-3-(2-ethoxyvinyl)furo[*3,2-b*]pyridine in moderate yields via elimination and isomerization (**Scheme 37**).[29]

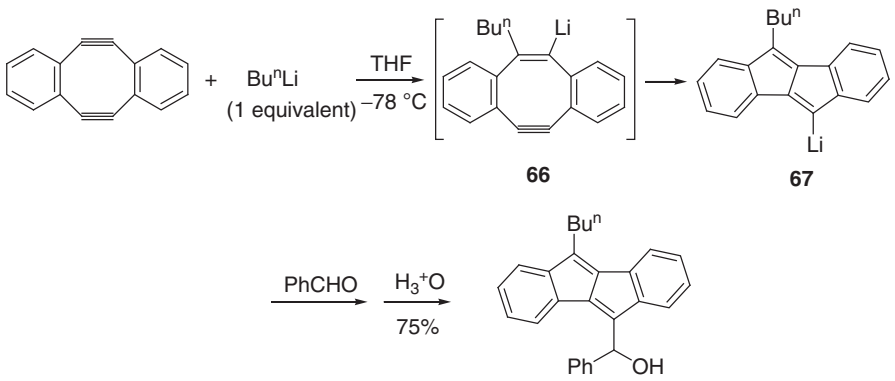
4.15.1.2.2.3 Cascade reactions

The intermolecular nucleophilic addition of primary alkyllithium to the highly strained 5,6,11,12-tetradehydrodibenzo[*a,e*]cyclooctene affords a vinyllithium intermediate **66** which subsequently undergoes the following intramolecular *trans*-annular addition with the other carbon–carbon triple bond to form the 9-lithiated-12-butyldiphensuccinda-9,11-diene **67**. This organolithium can react with a variety of electrophiles to yield the nucleophilic addition products (**Scheme 38**).[30]

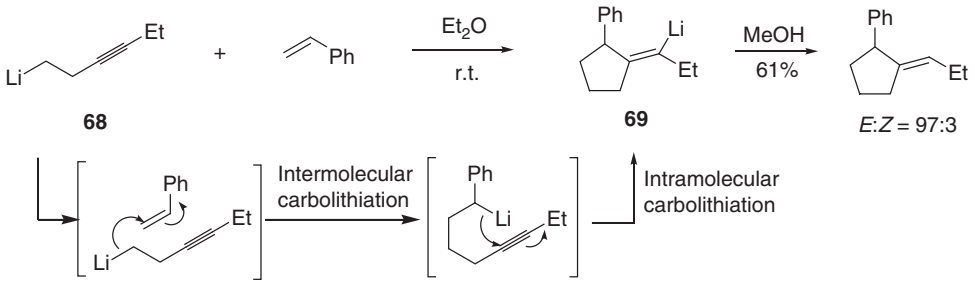
The inter–intramolecular carbolithiation of hex-3-ynyllithium **68** with styrene affords (cyclopentylidenemethyl)lithium **69** with high regio- and stereoselectivities (**Scheme 39**).[24]



Scheme 37



Scheme 38



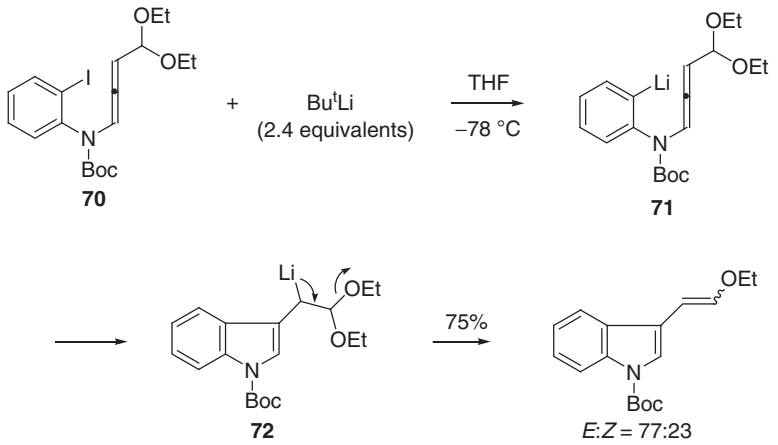
Scheme 39

4.15.1.2.3 The Carbolithiation of Allenes

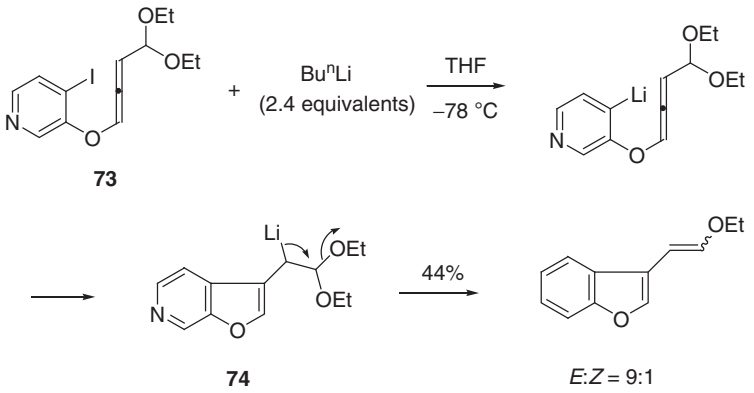
Treatment of 2-iodophenyl allenyl amine **70** with 2.4 equivalents of Bu^{t}Li at − 78 °C affords the iodine–lithium exchange product **71**. The subsequent intramolecular 5-*exo* carbolithiation of the allene moiety produces the allylic organolithium species **72** (Scheme 40).[29] A similar reaction of 4-iodo-3-pyridinyl allenyl ether **73** results in the corresponding allyllithium **74** via the same process (Scheme 41).[31]

4.15.1.3 The Carbomagnesiation Reaction

The addition of organomagnesium across carbon–carbon multiple bonds is a principal reaction in organic synthesis. Although the intramolecular carbomagnesiation remains undeveloped, it is still a very important and useful way to get alkyl or alkenyl magnesium reagents which can be further transformed into diverse functional groups. [32]



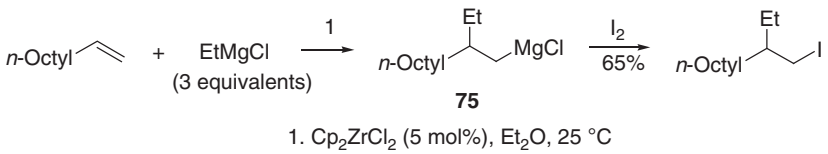
Scheme 40



Scheme 41

4.15.1.3.1 The Carbomagnesiation of Alkenes

The Zr-catalyzed ethylmagnesation of nonfunctionalized monosubstituted alkenes forms *n*-alkylmagnesium **75** with excellent regioselectivities (>99:1) (Scheme 42).[33]



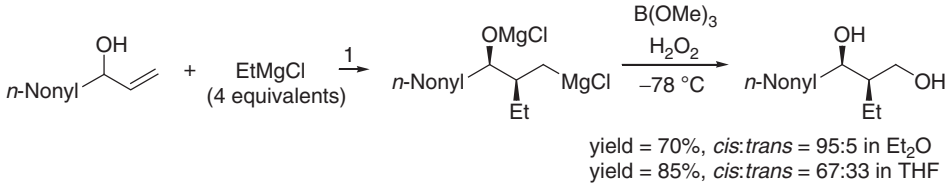
Scheme 42

A diastereoselective C–C bond formation is achieved by Zr-catalyzed ethylmagnesiation of allylic alcohols. An excess amount of EtMgCl is required, since deprotonation is the initial step followed by *syn*-addition which gives good regio- and diastereoselectivities. Considering the resulting selectivities, Et_2O is much better than THF. This may be because with more Lewis-basic THF as the solvent, the metal–heteroatom association is weaker, which results in the lower level of stereoselectivity control (Scheme 43).[33,34]

When allylic ethers are applied under identical conditions, the *trans*-product is formed as the major one in good yields. The different stereoselectivity may be due to the absence of oxygen–metal chelation (Scheme 44).[33,34]

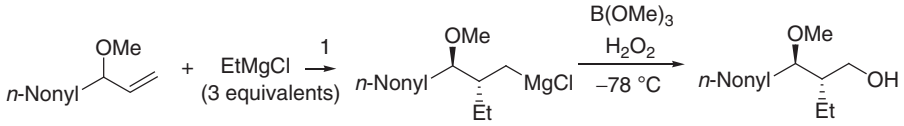
Although for homoallylic alcohols, instead of β-oxygen influence, the α-stereogenic center turns to be the primary reason for the stereochemistry. The carbon–carbon bond is formed *anti* to the α-methyl group from either *anti*- or *syn*-isomers. The only difference is that both the yield and diastereoselectivity are lower than that from the *syn*-isomer (Scheme 45).[34]

Under the catalysis of CuI, the *syn*-carbomagnesiation of cyclopropenylmethanol derivatives with *n*-alkyl or phenyl Grignard reagents affords α-hydroxyl cyclopropanylmagnesium **76** with high regio- and stereoselectivities (equation 5).[35]



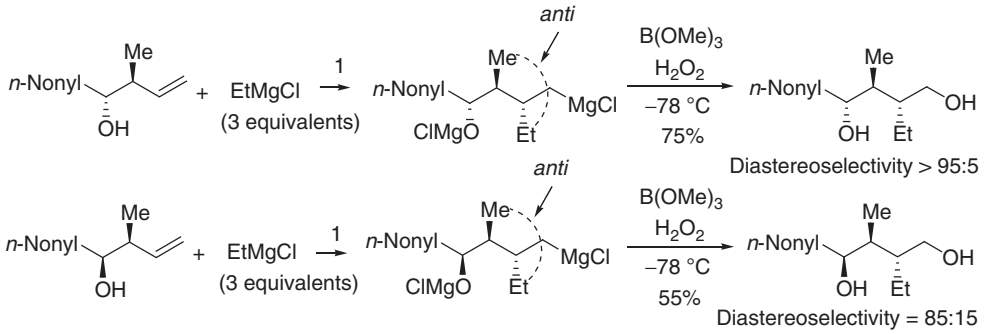
1. Cp_2ZrCl_2 (5 mol%), Et_2O or THF, 25 °C

Scheme 43



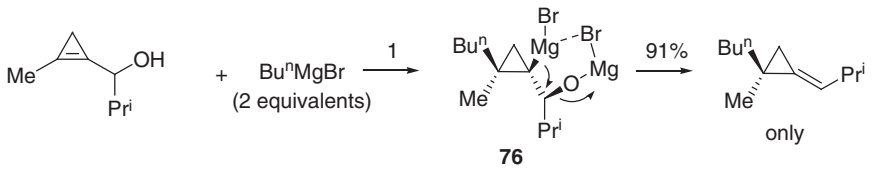
1. Cp_2ZrCl_2 (5 mol%), Et_2O or THF, 25 °C

Scheme 44



1. Cp_2ZrCl_2 (5 mol%), Et_2O or THF, 25 °C

Scheme 45



76

1. CuI (20 mol%), Et_2O, –50 °C to r.t.

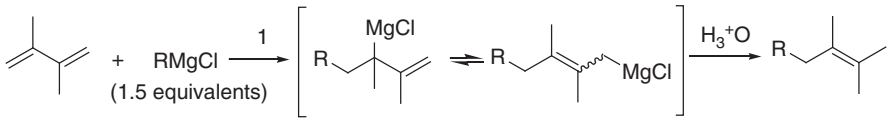
(5)

The Li_2CuCl_4-catalyzed carbomagnesiation of 2,3-dimethylbuta-1,3-diene affords an equilibrium of 1,2- and 1,4-adducts. However, only the 1,4-addition product is generated after hydrolysis. Tertiary alkyl Grignard reagents react faster than secondary ones. Primary alkyl Grignard reagents show no reactivity at all (Scheme 46).[36]

In the case of enynes, the addition takes place at the alkene moiety to form propargylmagnesium **77** which can be further transformed into the allenylic magnesium **78** via isomerization (Scheme 47).[36,37]

4.15.1.3.2 The Carbomagnesiation of Alkynes

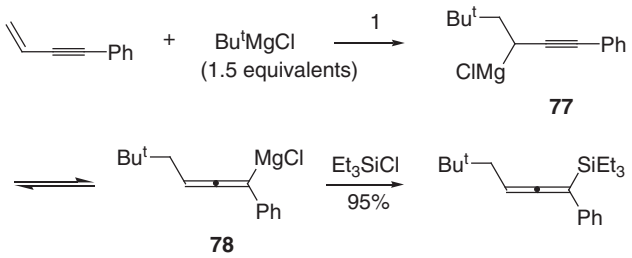
The carbomagnesiations of terminal alkynes in the absence of transition metal catalysts are rare, since terminal alkynes are readily deprotonated by organomagnesium. Under the catalysis of (IMes)AgCl (IMes = 1,3-dimesitylimidazol-2-ylidene), the addition of Grignard reagents to terminal alkynes affords *Z*-vinylic organomagnesium **79** with high regio- and stereoselectivities. In this catalytic system, neither aliphatic nor internal alkynes exhibit any reactivity. A series of primary, secondary, and tertiary alkyl



R = Bu^n, yield = 0%, conversion < 1%
R = Bu^s, yield = 27%, conversion < 34%
R = Bu^t, yield = 90%, conversion > 98%

1. Li_2CuCl_4 (1 mol%), THF, 25 °C, 3 h

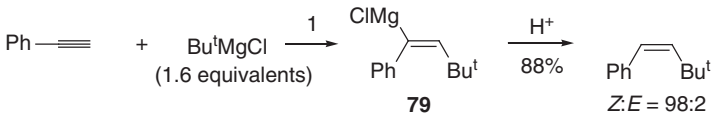
Scheme 46



1. Li_2CuCl_4 (1 mol%), THF, r.t.

Scheme 47

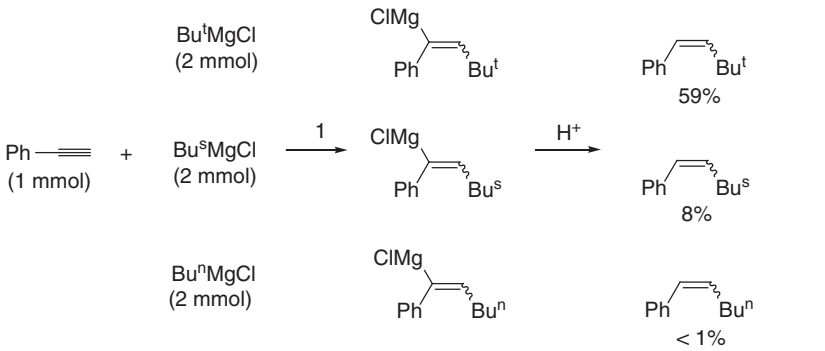
Grignard reagents can be applied in this reaction, however, no reaction takes place when methyl, benzyl, or phenyl Grignard reagents are used (Scheme 48).[37] Better stereoselectivities are obtained with greater steric resistance of the Grignard reagents.



1. (IMes)AgCl (5 mol%), $BrCH_2CH_2Br$ (1 equivalent), Et_2O, –10 °C

Scheme 48

When 2 equivalents of Bu^{t}MgCl, Bu^{s}MgCl, and Bu^{n}MgCl are added together in the reaction with phenylacetylene under standard conditions, a mixture of vinylmagnesium are formed respectively, in which the Bu^{t}MgCl addition product is the major one, indicating that tertiary alkyl Grignard reagents are much more reactive than others (Scheme 49).[37]

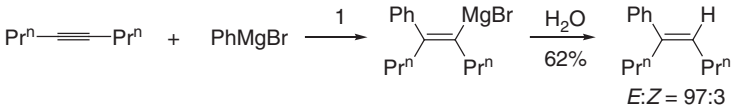


Z/E ratio was not determined

1. (IMes)AgCl (5 mol%), $BrCH_2CH_2Br$ (2 equivalents), Et_2O, –10 °C, 3 min

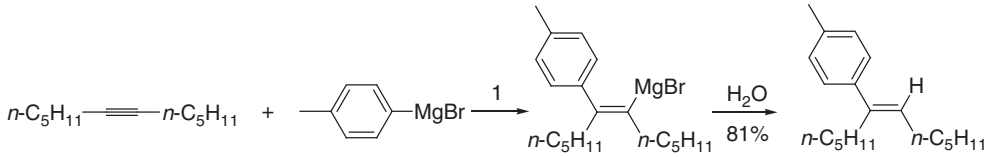
Scheme 49

In the presence of iron,[38,39] copper,[38] manganese,[40] or cadmium,[41] the carbomagnesiation of nonfunctionalized internal alkynes takes place via the *syn*-model, affording *E*-alkenylmagnesium as the major adduct in good to high yields (Schemes 50 and 51).[38,41] When aryl(alkyl)acetylenes are applied, the magnesium atom is selectively installed to the aryl side (Schemes 52 and 53).[39,40]



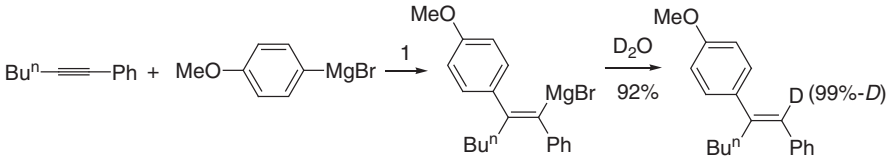
1. $Fe(acac)_3$ (5 mol%), CuBr (10 mol%), PBu^n_3 (40 mol%), THF, 60 °C

Scheme 50

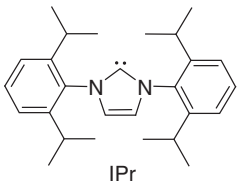


1. $CrCl_2$ (7.5 mol%), Bu^tCOOH (10 mol%), toluene, 110 °C

Scheme 51

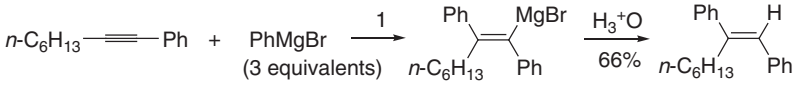


1. $Fe(acac)_3$ (5 mol%), IPr (20 mol%), THF, 60 °C



IPr

Scheme 52

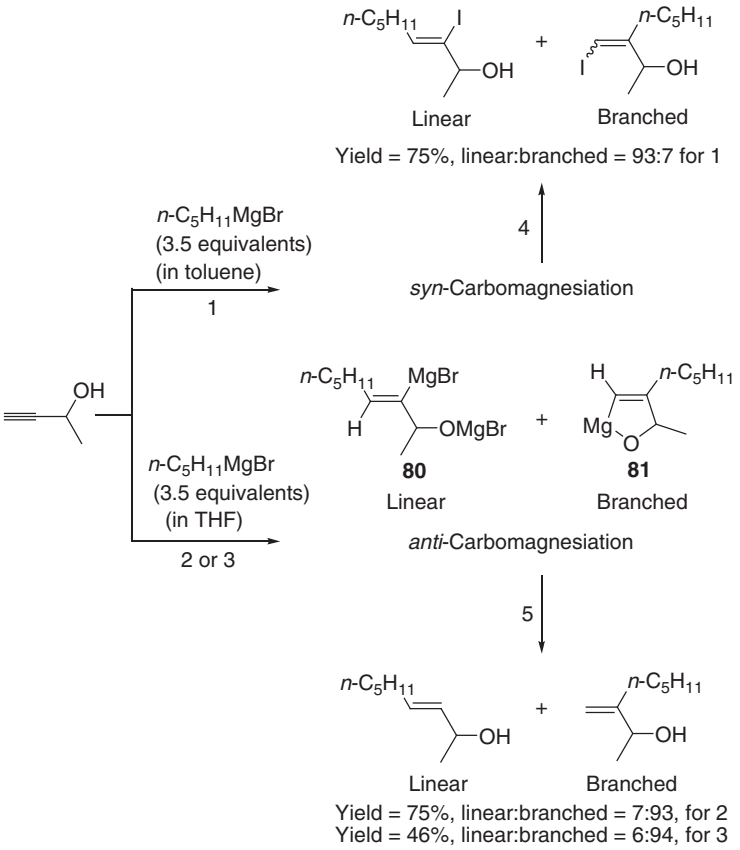


1. $MnCl_2$ (10 mol%), toluene, 100 °C

Scheme 53

The copper(I)-mediated or catalyzed carbomagnesiation of terminal propargylic alcohols with primary alkyl or phenylmagnesium bromides affords a mixture of linear isomer **80** and branched isomer **81**. Solvent effect is crucial in controlling the regio- and stereoselectivities. For *syn*-carbomagnesiation, **80** is formed as the major product. To achieve high selectivities, the Grignard reagents must be prepared first in Et_2O followed by adding toluene and heating at 120 °C for 0.5 h to remove all of the Et_2O solvent, then treated with CuI (1.0 equivalent based on the alcohol) in toluene at 25 °C before the alcohol is added (Scheme 54).[42] When the Grignard reagents are prepared in THF, the *anti*-carbomagnesiation proceeds smoothly in the presence

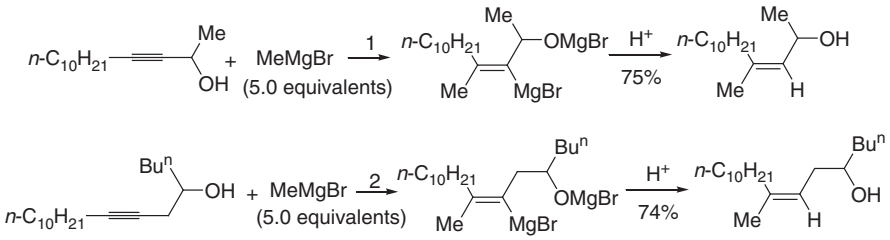
of a catalytic amount of copper(I) salt, resulting in the same isomeric mixture. However, the selectivities changed dramatically, yielding the branched adduct **81** as the major one (Scheme 54).[43] Two reaction conditions (Conditions A: CuI (50 mol%), toluene, −78 °C to room temperature; Conditions B: CuCl (10 mol%), toluene, −78 °C to room temperature) are established to control the regio- and stereoselectivities. For Conditions B, less amount of catalyst is used with slightly higher selectivities observed; however, in contrast with Conditions A, the yields are obviously lower.



1. CuI (1.0 equivalent), toluene, –40 °C to r.t.; 2. CuI (50 mol%), toluene, –78 °C to r.t.;
3. CuCl (10 mol%), toluene, –78 °C to r.t.; 4. I_2 (3.5 equivalents), Et_2O, –40 °C; 5. NH_4Cl/H_2O, 0 °C

Scheme 54

In the presence of an iron compound as the catalyst, the additions to internal propargylic or homopropargylic alcohols occur readily via the *syn*-process, yielding tetrasubstituted vinylic magnesium species as a single regio- and stereoisomer (Scheme 55).[44] Both primary and secondary alcohols are tolerated.

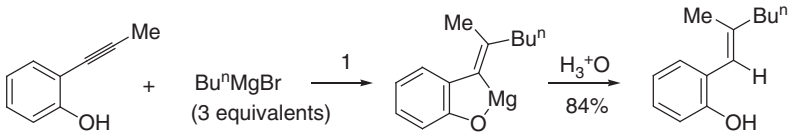


1. $Fe(ehx)_3$ (20 mol%), dppe (20 mol%), THF, 0 °C; 2. $Fe(acac)_3$ (20 mol%), THF, 0 °C

Scheme 55

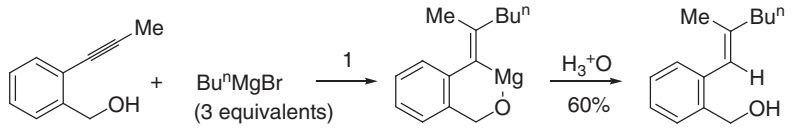
2-Alkynylphenols give *E*-alkenylmagnesium reagents as the major product via the *syn*-addition model at room temperature (Scheme 56).[45] Notably, the hydroxyl group not only helps control the regio- and stereoselectivities, but also plays a key role in

the reactivity. Without the hydroxyl group, this reaction provides a very low yield. In addition, the position of the hydroxyl group on the phenyl ring is also crucial. Only 2-alkynylphenols are reactive. The general scope of the Grignard reagents is good, alkyl-, allyl-, and phenylmagnesium reagents are all accommodated. Surprisingly, 2-alkynyl benzyl alcohols are also reactive and give even better stereoselectivities (Scheme 57).[45]



1. $MnCl_2$ (10 mol%), toluene, 25 °C

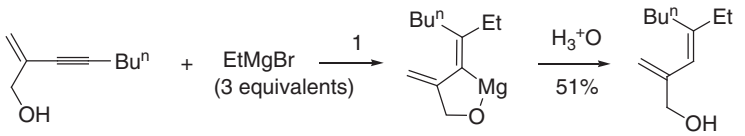
Scheme 56



1. $MnCl_2$ (10 mol%), toluene, 25 °C

Scheme 57

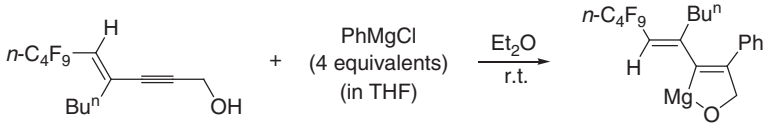
Similarly, at a higher reaction temperature, the reaction of 2-methylene-3-octyn-1-ol derivatives with alkyl Grignard reagents yields the *syn*-addition products via a five-membered ring intermediate with excellent regio- and stereoselectivities (Scheme 58).[45]



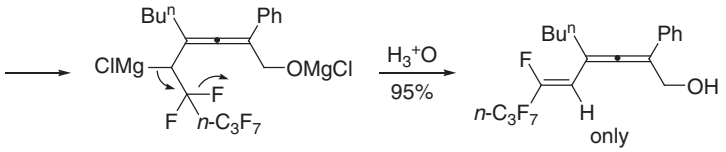
1. $MnCl_2$ (10 mol%), toluene, 50 °C

Scheme 58

In contrast, the addition to 5-perfluoroalkylsubstituted 4(*E*)-alken-2-ynols affords vinylic organomagnesium intermediate **82** via an *anti*-addition process, which isomerizes easily to form the magnesiated allene derivatives **83**. Subsequent *anti*-defluorometallation leads to the formation of 6-perfluoroalkyl-6-fluoroalka-2,3,5(*Z*)-trienols highly *Z*-selectively (Scheme 59).[46]



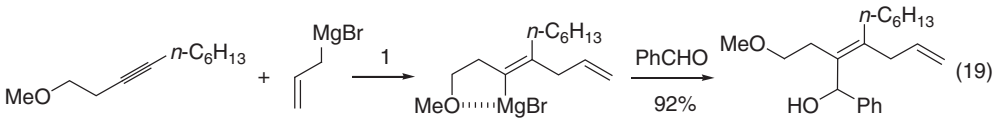
82



83

Scheme 59

The oxygen-assistance sometimes helps to control the regioselectivity efficiently. For example, the allylmagnesium bromide undergoes *syn*-addition with 1-methoxydec-3-yne, yielding (*Z*)-(4-allyl-1-methoxydec-3-en-3-yl) magnesium bromide **84** as the sole product (Scheme 60).[47]

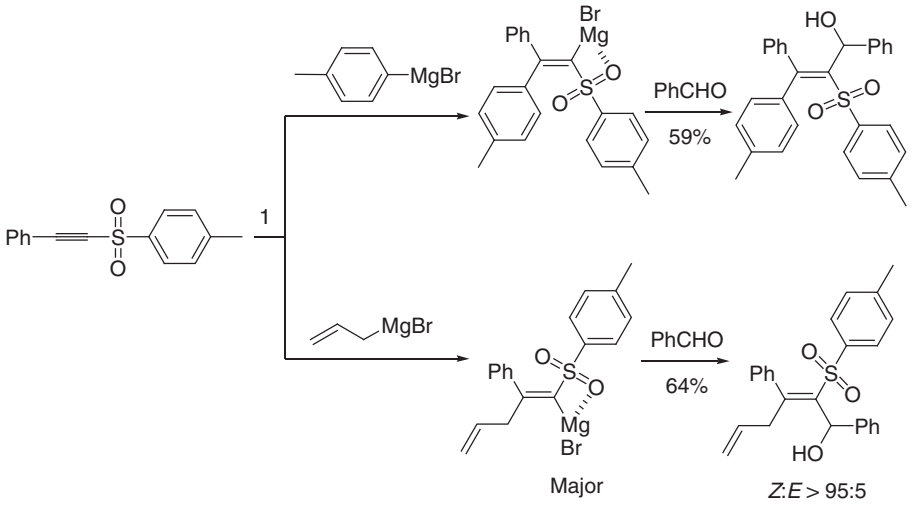


84

1. MnI_2 (3 mol%), Et_2O, 25 °C

Scheme 60

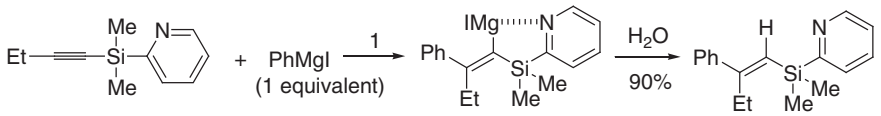
Another example of the oxygen-directing effect is observed in the carbomagnesiation of 1-(1-methyl-4-(phenylsulfonyl))-2-phenylacetylene. The magnesium atom is mainly attached to the α-position of the sulfone group. The stereoselectivities are highly substrate dependent. When aryl Grignard reagents are applied, only the *E*-isomers are formed; however, if allylic Grignard reagents are used, a mixture of *Z*- and *E*-isomers are produced, in which the *Z*-isomer is the major one (Scheme 61).[48]



1. CuCN (10 mol%), THF/CH_2Cl_2 = 1:4, –20 °C

Scheme 61

The arylmagnesium iodides react with 1-butynyl dimethyl (2-pyridyl)silane in the presence of 30 mol% of CuI to give the corresponding alkenylmagnesium iodides **85** with high regio- and stereoselectivities (Scheme 62).[49] Notably, when 3-pyridyl, 4-pyridyl, or phenyl silanes are applied as the reactant, no reaction takes place at all. Obviously, the 2-pyridyl group shows a strong directing effect in this reaction, which not only results in the high selectivity, but also improves the reactivity. With an equimolar amount of CuI, no reaction occurs, which means the organocuprates formed *in situ* might be the reactive intermediates. The arylmagnesium iodides are more reactive than their bromide and chloride analogs.



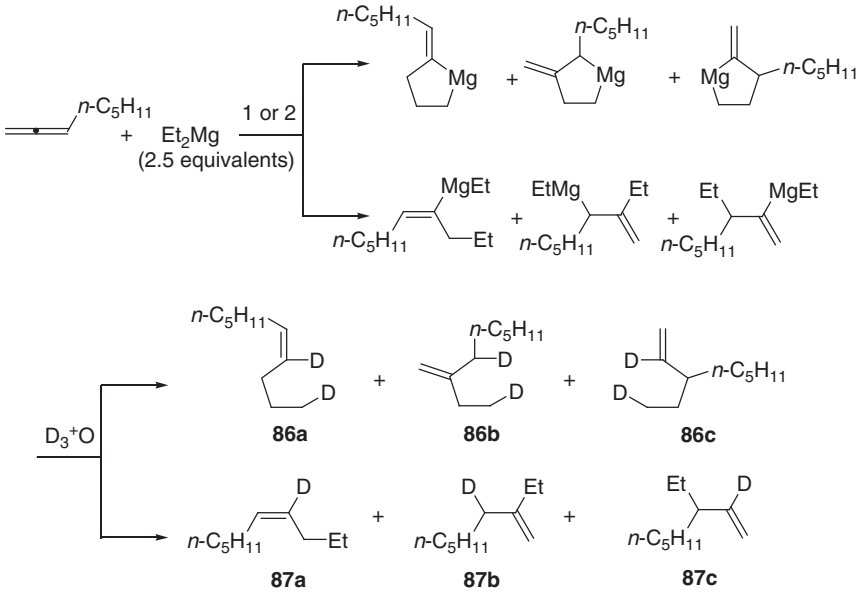
85

1. CuI (30 mol%), Et_2O, 0 °C

Scheme 62

4.15.1.3.3 The Carbomagnesiation of Allenes

The reaction of alkylallenes with Et_2Mg catalyzed by Cp_2ZrCl_2 leads to the formation of a mixture of cyclomagnesiation and carbomagnesiation products. The solvent effect in this reaction is clear. When the reaction is carried out in Et_2O, **86** is the major product with a ratio of **86**:**87** = 6:1. When THF is used as the solvent, the ratio changes into **86**:**87** = 1:8 (Scheme 63).[50]

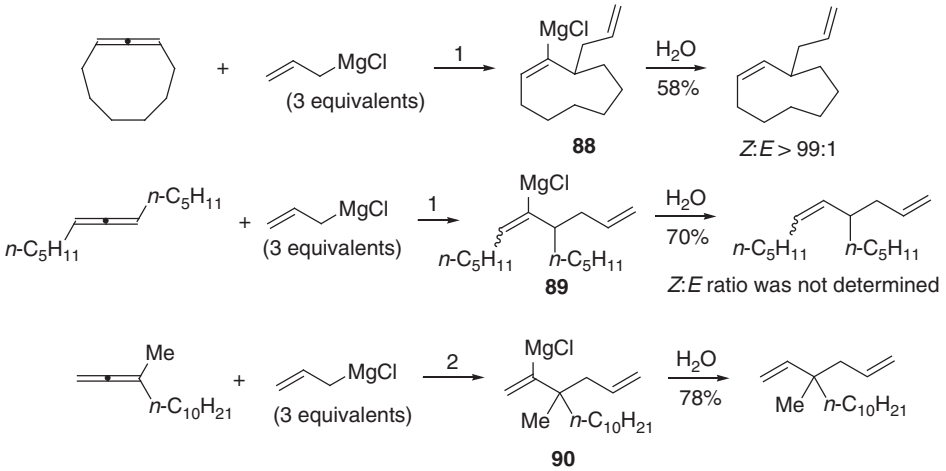


Yield = 80%, **86**:**87** = 6:1 for 1
Yield = 80%, **86**:**87** = 1:8 for 2

1. Cp_2ZrCl_2 (5 mol%), Et_2O, 0 °C; 2. Cp_2ZrCl_2 (5 mol%), THF, 0 °C

Scheme 63

The Mn-catalyzed allylmagnesiation of cyclic allenes affords cyclic alkenylmagnesium species **88**. Although for the reaction of acyclic allenes, the corresponding vinylmagnesium reagents **89** or **90** are formed. In all cases, the magnesium atom is located at the middle carbon atom of the allene moiety (Scheme 64).[51]

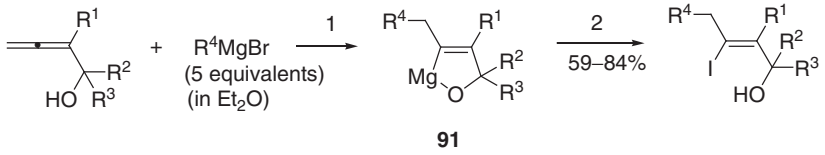


1. $MnCl_2$ (20 mol%), THF, r.t.; 2. $MnCl_2$ (20 mol%), HMPA (2.0 equivalents), THF, r.t.

Scheme 64

The CuCl-mediated carbomagnesiation of 2,3-allenols with Grignard reagents produces the alkenylmagnesium species **91** in high regio- and stereoselectivities. The R^4 group in the Grignard reagents is attached to the terminal position of the allene moiety.

And the magnesium atom settles down at the middle carbon of the allene moiety at the *cis*-position of the hydroxyl group (Scheme 65).[52]



91

R^1 = H, Bu^n, phenyl, or allyl
R^2 = H, Me, or phenyl
R^3 = H or Me
R^4 = *n*-C_5H_{11}, Cy, Bu^i, or aryl

1. CuCl (2 equivalents), Et_2O, –78 °C to r.t.; 2. I_2 (5 equivalents), THF, –5 °C

Scheme 65

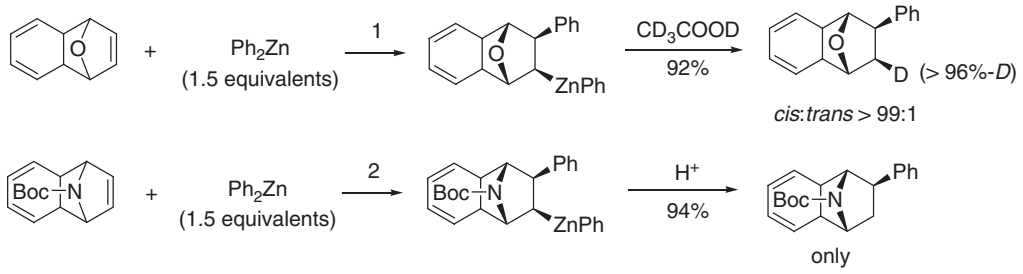
4.15.1.4 The Carbozincation Reaction

4.15.1.4.1 The Carbozincation of Alkenes

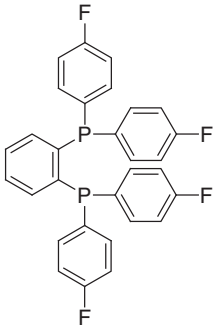
4.15.1.4.1.1 Intermolecular reactions

The scope of intermolecular carbozincation with alkenes is a little limited. As reported, di-*tert*-butyl and diallyl zinc species as well as allylic zinc halides show good reactivities in such reactions, whereas other types of organozinc reagents are commonly inert especially for nonfunctionalized alkenes.[53] New developments in this field that are not introduced in the first edition are not numerous. Two typical results are selected and shown as follows.

In the presence of a catalytic amount of electron-deficient diphosphine ligand 1,2-bis(bis(4-fluorophenyl)phosphino)benzene (BBFFB), the Fe(III)-catalyzed highly diastereoselective carbozincation of oxa- or azabicyclic alkenes with diarylzinc reagents affords the corresponding cyclic alkylzinc species via the *syn*-addition process (Scheme 66).[54]



1. $FeCl_3$ (1 mol%), BBFFB (2 mol%), THF/toluene = 1:1, 0 °C
2. $FeCl_3$ (3 mol%), BBFFB (6 mol%), THF/toluene = 1:1, 40 °C

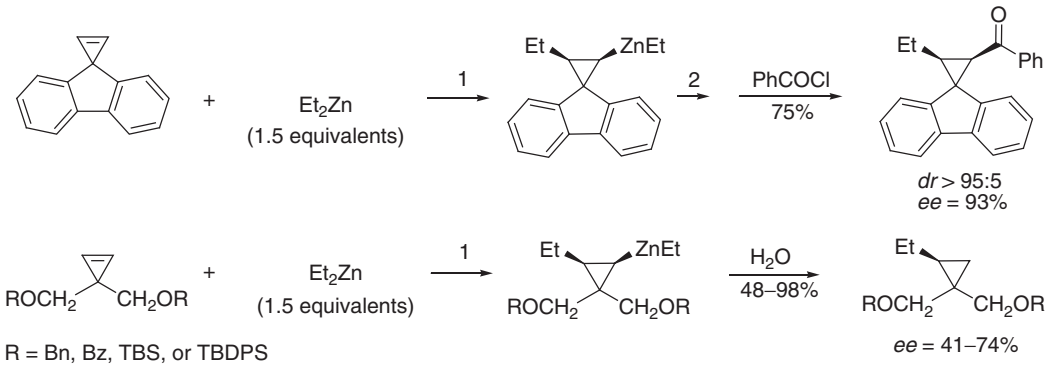


BBFFB

Scheme 66

The Pd-catalyzed enantio- and diastereoselective carbozincation of cyclopropenes with Et_2Zn in the presence of (*R*)-tol-BINAP and $Zn(OTf)_2$ in CH_2Cl_2 occurs at low temperatures. The solvent effect is crucial. If more coordinating solvents such as THF or

N-methyl-2-pyrrolidone are applied, the catalysis is dramatically inhibited. The addition of $Zn(OTf)_2$ increases the reaction speed of the carbozincation step. The generality of this protocol is a little limited. Only spiro(2-cyclopropene-1,9'-(9*H*)fluorine) gives a quantitative yield with a *dr* value of >95:5 and an *ee* value of >90%. When 3,3-dimethylcycloprop-1-ene derivatives are used as the reactants, the yields and/or selectivities are not satisfying (Scheme 67).[55]

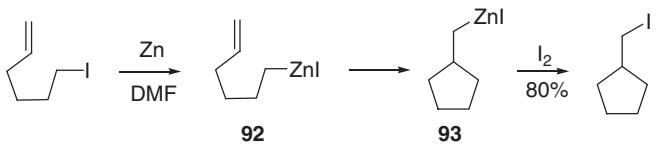


1. $Pd(MeCN)_2Cl_2$ (5 mol%), (*R*)-tol-BINAP (6 mol%), $Zn(OTf)_2$ (10 mol%), CH_2Cl_2, –78 °C to r.t.
2. CuCN·2LiCl, THF, –78 °C

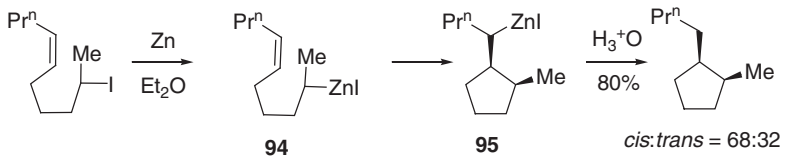
Scheme 67

4.15.1.4.1.2 Intramolecular reactions

The intramolecular carbozincation of 6-iodohex-1-ene derivatives was studied carefully by Marek and coworkers The 5-hexen-1-ylzinc iodide **92**, which is prepared *in situ* by the reaction of 6-iodohex-1-ene with activated zinc, undergoes regiospecific 5-*exo* cyclization to form (cyclopentylmethyl)zinc iodide **93** as the only product (Scheme 68).[56] When *n*-propyl group is introduced to the terminal position of the alkene moiety, the carbozincation of **94** leads to a new secondary zinc iodide **95** which can be readily hydrolyzed to produce 1-butyl-2-methylcyclopentane in 80% yield with a *cis*:*trans* diastereomeric ratio of 68:32 (Scheme 69).[56]



Scheme 68

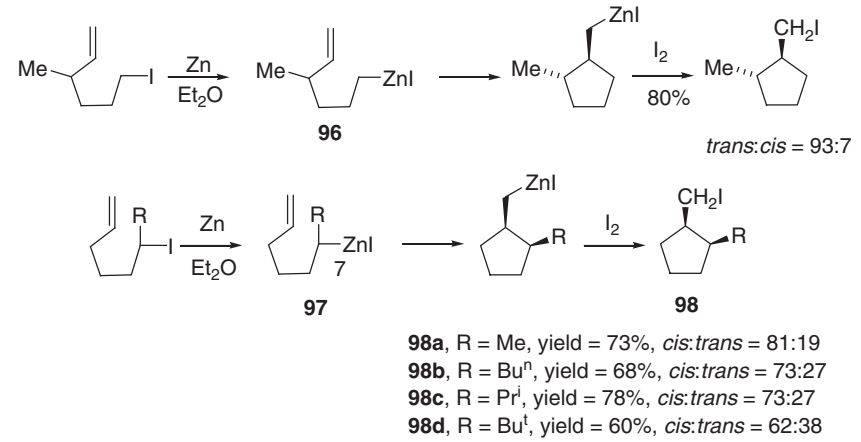


Scheme 69

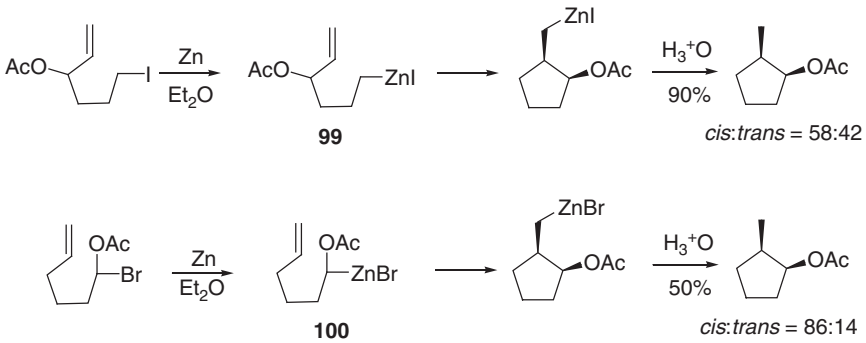
The 3- or 6-alkylsubstituted olefinic organozinc iodide **96** or **97** undergoes anionic cyclization smoothly, yielding 1,2-disubstituted cyclopentanes after iodinolysis (Scheme 70).[56] However, the stereoselectivities appear contrary to each other. (4-Methylhex-5-enyl)zinc iodide **96** prefers *trans*-addition, whereas hept-6-en-2-ylzinc iodide **97** gives the *cis*-cyclized product **98** as the major one. This is of great synthetic value, since two diastereoisomers can be prepared easily from different reactants. Furthermore, the scope of this reaction is quite broad, the 6-alkyl group can be primary, secondary, and tertiary. However, with bulkier steric hindrance, the *cis*:*trans* ratio goes down sharply.

Under the same conditions, the reaction of 3- or 6-acetoxysubstituted olefinic organozinc compounds **99** or **100** undergoes *cis*-preferred intramolecular carbozincation, forming a mixture of stereoisomers. The secondary organozinc intermediate **100** gives a better stereoselectivity (Scheme 71).[56]

The zincation of 4-iodonona-1,8-diene **101** generates nona-1,8-dien-4-ylzinc iodide **102** which forms a mixture of *trans*- and *cis*-isomers **103** via intramolecular cyclization. The second intramolecular carbozincation of ***cis*-103** leads to the formation of the

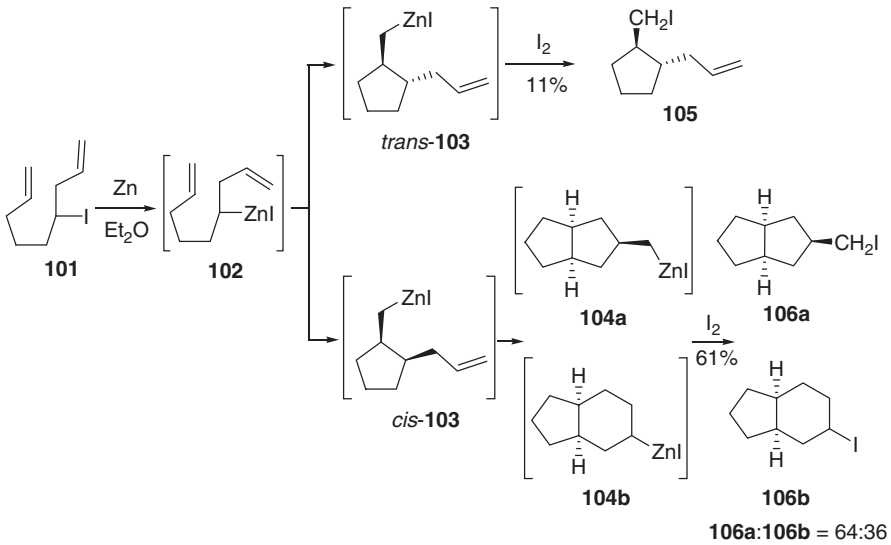


Scheme 70



Scheme 71

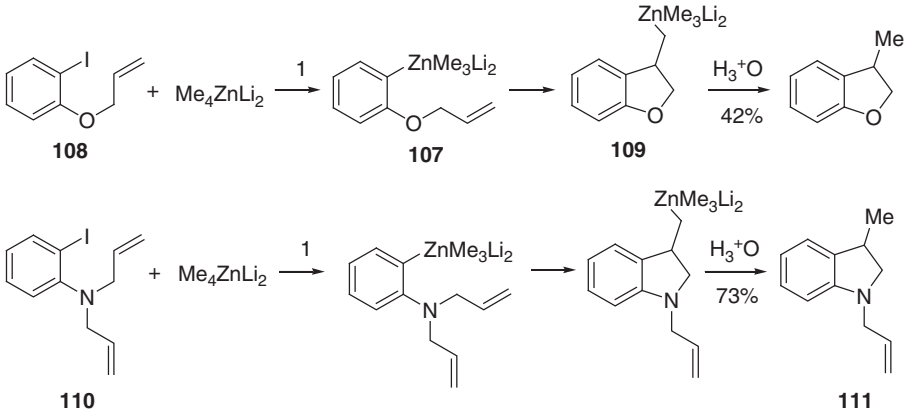
bicyclic zinc intermediate **104**. Iodinolysis of the organozinc mixture results in 11% of **105** and 61% of **106** with an *exo*:*endo* ratio of 64:36 (Scheme 72).[56]



Scheme 72

Uchiyama and Sakamoto et al. designed a new category of zincate species and successfully applied them to the intramolecular carbozincation of allyl 2-zincatedphenyl ether **107** which is prepared *in situ* from the iodine–zinc exchange of allyl 2-iodophenyl

ether **108** with Me_4ZnLi_2. The highly regioselective cyclization forms the zincate **109** via 5-*exo* process, which gives 3-methyl-2,3-dihydrobenzofuran in 40% isolated yield after hydrolysis. *N*,*N*-Diallyl-2-iodobenzenamine **110** can also be applied in this reaction, yielding 1-allyl-3-methylindoline **111** via the same process (Scheme 73).[57]



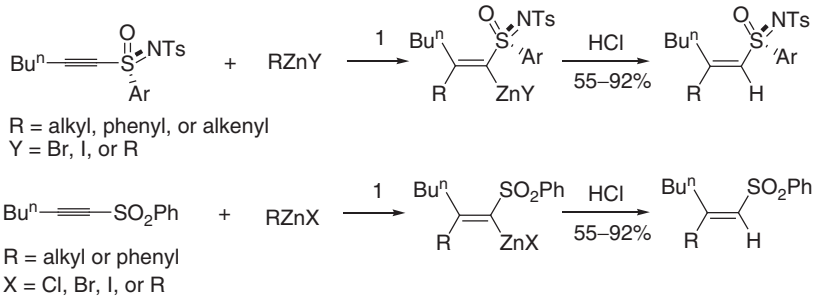
1. THF, 0 °C, 2 h, then r.t., 48 h

Scheme 73

4.15.1.4.2 The Carbozincation of Alkynes

4.15.1.4.2.1 Intermolecular reactions

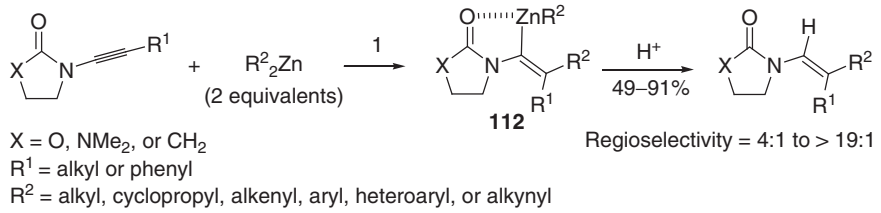
The copper-catalyzed carbozincation of alkynylsulfoximines[58] or alkynylsulfones[59] with organozinc halides or dialkylzinc affords alkenylzinc reagents as a single stereoisomer via the *syn*-addition process under mild conditions in either THF or Et_2O. The zinc atom is regioselectively attached to the sulfur side of the carbon–carbon triple bond (Scheme 74).



1. CuI (10 mol%), THF, 0 °C

Scheme 74

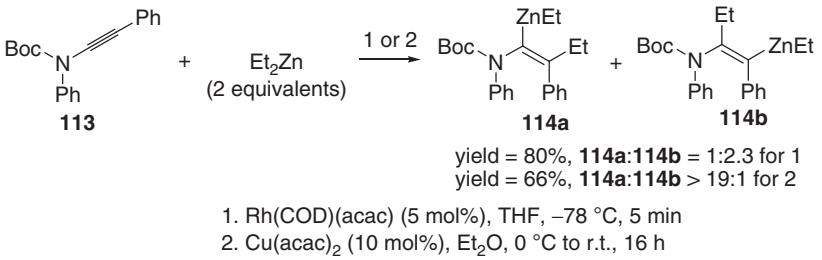
The Rh-catalyzed highly regio- and stereoselective carbozincation of cyclic ynamides with diorganozinc forms alkenylzinc **112** (Scheme 75).[60] The scope of this reaction is quite broad. The ynamides containing oxazolidin-2-one, pyrrolidin-2-one, or urea functionalities are all reactive. Both alkyl and phenyl groups on the alkyne moiety are tolerable. A large variety of zinc reagents can be applied in this reaction. In all cases, the carbonyl-directed *syn*-addition process is favored, providing good to excellent selectivities. However, the reaction of acyclic ynamides under the same conditions gives unsatisfying results. Although the



1. Rh(COD)(acac) (5 mol%), THF, 0 °C to r.t.

Scheme 75

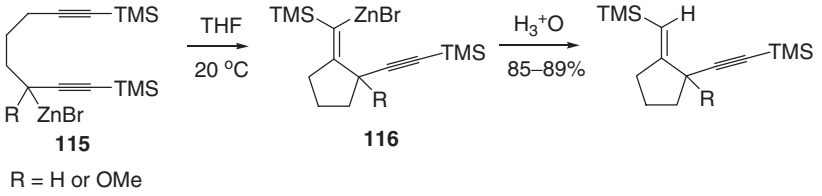
carbozincation of **113** proceeds rapidly even at low temperatures in good yields, the opposite regioisomer **114b** is favored with poor regioselectivity. When 10 mol% of $Cu(acac)_2$ is used instead of Rh(COD)(acac) in Et_2O, the reaction proceeds slowly and results in much lower yield, however, an excellent regioselectivity of >19:1(**114a**:**114b**) is observed (Scheme 76).[60]



Scheme 76

4.15.1.4.2.2 Intramolecular reactions

The 3-zincated 1,8-bis(trimethylsilyl)octa-1,7-diynes **115** undergo intramolecular *syn*-carbozincation via 5-*exo* fashion, affording the configurationally stable (*Z*)-alkenylzinc bromides **116** as the sole product (Scheme 77).[61]



Scheme 77

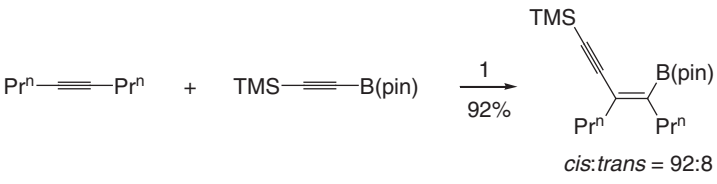
The carbozincation of allylic zinc bromides to the intramolecular internal carbon–carbon triple bond forms the corresponding monocyclic alkenylzinc bromides (Scheme 78).[62] The reaction speed and required reaction temperature are dependent on the ring size. The reaction for the construction of a five-membered ring completes within 2 h at room temperature. However, for six- or seven-membered ring systems, higher temperature and longer reaction time are required. In this transformation, no direct intramolecular carbozincation occurs at all. Instead, an allylic isomerization which results in the formation of the reactive allylzinc intermediates is the initial step. Then the subsequent cyclization yields the cyclic alkenylzinc bromides.

4.15.1.5 The Carboboration Reaction

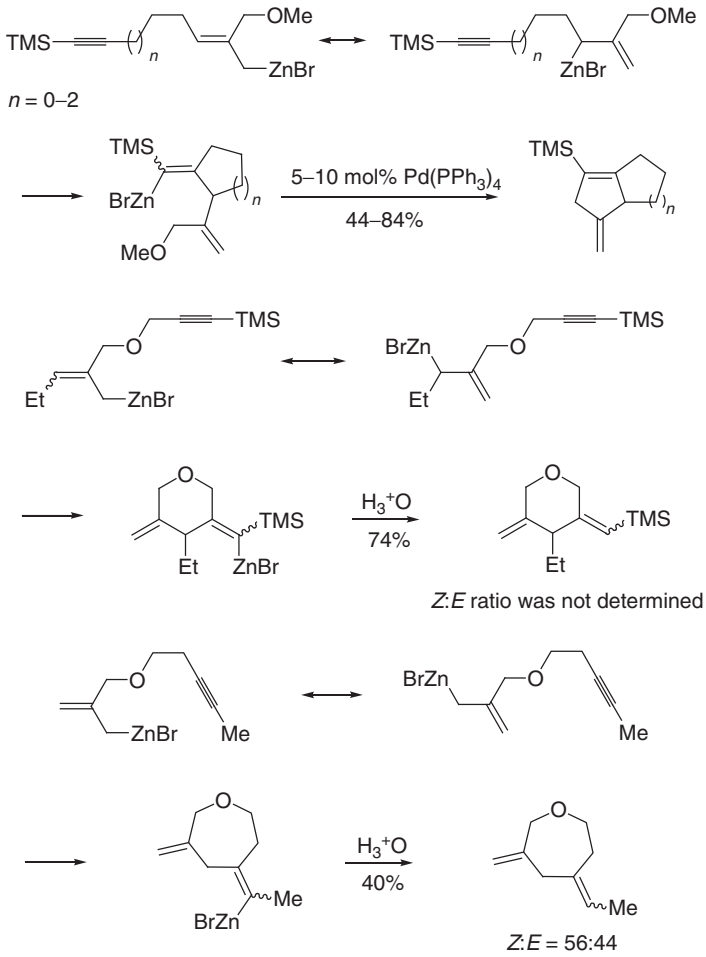
4.15.1.5.1 The Carboboration of Alkynes

Palladium is found to be efficient for catalyzing the intermolecular cyanoboration of cyclic cyannoborane derivatives to non-functionalized alkynes (Scheme 79).[63] Only *cis*-addition products are formed in this reaction. The addition to 4-octyne affords *cis*-*β*-cyano-*α*,*β*-unsaturated borane derivative. Under the same conditions, the reaction of unsymmetrical alkynes that bear both aryl and alkyl groups at their sp-hybridized carbon atoms gives a mixture of regioisomers. For the main product, the cyano group is attached to the *α*-carbon atom of the aryl group. Terminal alkynes can also be applied in this reaction, affording *cis*-adducts with good selectivities.

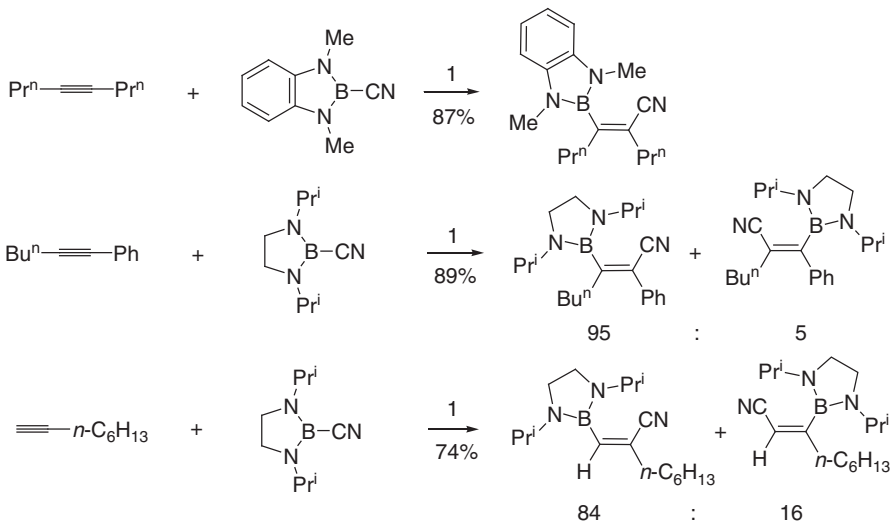
Nickel is another option for catalyzing the intermolecular carboboration of alkynes with alkynylborane. The reaction of symmetrical alkynes affords *cis*-addition products with high stereoselectivities (equation 6).[64] With unsymmetrical alkynes, both the yield and selectivities are poorer. For example, the reaction of 1-phenylhex-1-yne gives a mixture of alkenylboranes in 68% isolated yield with a regioselectivity of 93:7 and a stereoselectivity of 89:11 (equation 7).[64]



(6)

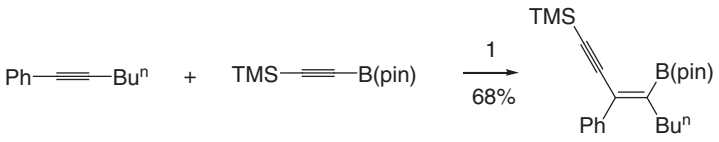


Scheme 78



1. [CpPd(η^3-C_3H_5)] (5 mol%), PMe_3 (15–20 mol%), dioxane, 130 °C

Scheme 79

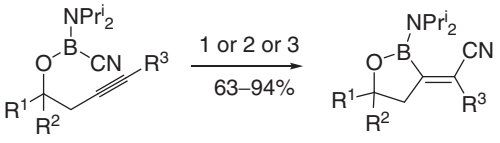


(7)

Regioselectivity = 93:7
cis:*trans* = 89:11

1. $Ni(COD)_2$ (5 mol%), PCy_3 (20 mol%), toluene, 80 °C

With palladium or nickel as the catalyst, the intramolecular cyanoboration of homopropargylic cyanoboryl ethers **117** affords 3-methylene-1,2-oxaborolane derivatives **118** via *cis*-addition process in a regioselective 5-*exo* fashion (Scheme 80).[65] The scope of this reaction is quite broad. Primary, secondary, and tertiary homopropargylic ethers having a terminal or internal carbon–carbon triple bond are all well tolerated. Notably, enyne **119** undergoes this intramolecular carboboration with the alkyne moiety under the catalysis of $Pd(PPh_3)_4$ to form 3-allylidene-1,2-oxaboralane derivative **120** in good yield with high regio- and stereoselectivity (equation 8).[65]

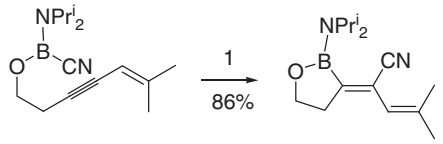


117 **118**

$R^1 = R^2 = -(CH_2)-_5$, R^3 = H or Et
$R^1 = R^2$ = H or Me, R^3 = Et or Ph
R^1 = Et, R^2 = H, R^3 = H or Me
R^1 = Et or Pr^n, R^2 = H or Me, R^3 = H or Me

1. $Pd_2(dba)_3$ (5 mol%), toluene, 80 °C
2. $Pd(PPh_3)_4$ (5 mol%), toluene, 110 °C
3. $Ni(COD)_2$ (5 mol%), toluene, 110 °C

Scheme 80



119 **120**

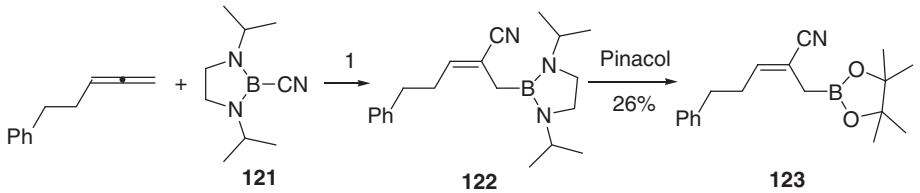
E:*Z* = 93:7

(8)

1. $Pd(PPh_3)_4$ (5 mol%), toluene, 110 °C

4.15.1.5.2 The Carboboration of Allenes

Under the catalysis of $CpPd(\eta^3\text{-}C_3H_5)$, the cyanoborane **121** reacts with terminal allenes at 130 °C in the presence of 5 mol% of PMe_3, producing (*E*)-*β*-cyanoallylborane **122** stereoselectively, which can be converted into allylborolane **123** in a low yield by treating with pinacol. The addition proceeds regioselectively at the terminal carbon–carbon double bond of the allene moiety with the cyano group introduced to the middle carbon atom and the boryl group attached to the terminal carbon atom (Scheme 81).[66]

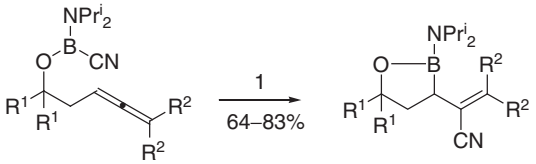


121 **122** **123**

1. $CpPd(\eta^3\text{-}C_3H_5)$ (5 mol%), PMe_3 (5 mol%), dioxane, 130 °C

Scheme 81

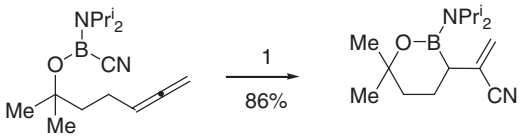
Under the same conditions, the intramolecular carboboration of **124** takes place to yield five-membered boranes **125** (Scheme 82).[66] The cyano group is attached to the middle carbon atom of the allene moiety as observed in the intermolecular reaction, however, the new carbon–boron bond is formed at the internal carbon atom of the allenyl group. Not only terminal, but also internal allenes can be used in this reaction. However, only the cyanoboryl ethers derived from tertiary alcohols are reactive. The substrates derived from primary and secondary alcohols show no reactivity at all. If homologous allenyl boryl ether **126** is used as the reactant, the six-membered ring product **127** will be formed in good yield (equation 9).[66]



124 **125**

R^1 = Ph, Me, Et, or -(CH_2)-$_4$, R^2 = H
$R^1 = R^2$ = Me
1. CpPd(η^3-C_3H_5) (5 mol%), PMe_3 (5 mol%), toluene, 80–130 °C

Scheme 82



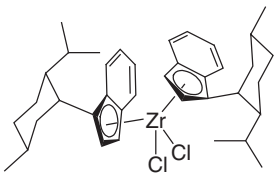
126 **127** (9)

1. CpPd(η^3-C_3H_5) (5 mol%), PMe_3 (5 mol%), toluene, 80–130 °C

4.15.1.6 The Carboalumination Reaction

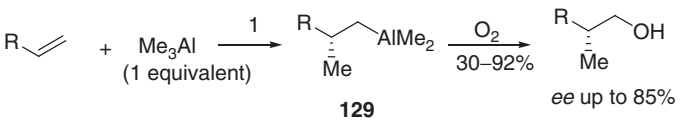
4.15.1.6.1 The carboalumination of alkenes

Dichlorobis(1-neomenthylindenyl)zirconium **128** (Scheme 83)[67] can catalyze the enantioselective methylalumination of monosubstituted simple alkenes without heteroatom functional groups, affording chiral 2-methylalkylaluminum species **129**, which can be easily converted into chiral 2-methyl-1-alkanols by oxidation with O_2 (Scheme 84).[67] Some other alkenes containing oxygen or nitrogen atom also undergo this methylalumination in good yields with good enantioselectivities (Scheme 85).[67]



128

Scheme 83



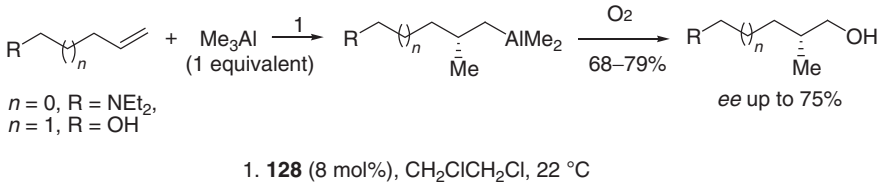
129

ee up to 85%

R = alkyl or aryl

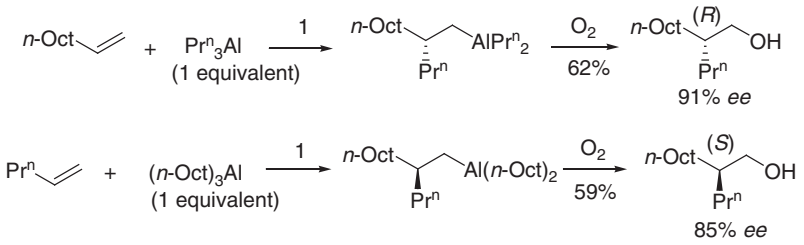
1. **128** (8 mol%), CH_2ClCH_2Cl, 22 °C

Scheme 84



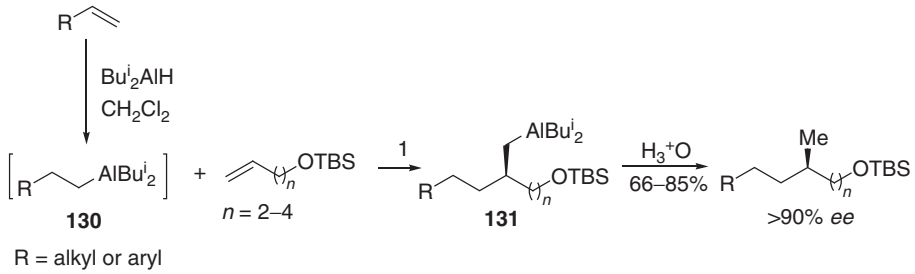
Scheme 85

This methylalumination can be extended to other alkylalumination by simply applying other trialkylalanes under similar conditions. Interestingly, both (*R*)- and (*S*)-2-propyl-1-decanol can be prepared by propylalumination of 1-decene or octylalumination of 1-pentene under identical conditions (Scheme 86).[68]



Scheme 86

Catalyst **128** is also efficient for the enantioselective hydroalumination/Zr-catalyzed alkylalumination tandem reaction in the presence of isobutylaluminoxane (Scheme 87).[69] This reaction initiates from the hydroalumination of alkenes with Bu^i_2AlH, yielding alkyldiisobutylalanes **130** which subsequently react with ω-alkenyl silyl ethers to form the chiral organoaluminum **131** in high regio- and enantioselectivities. The new carbon–aluminum bond is formed only at the terminal position of the carbon–carbon double bond which results in a chiral methyl group after hydrolysis.



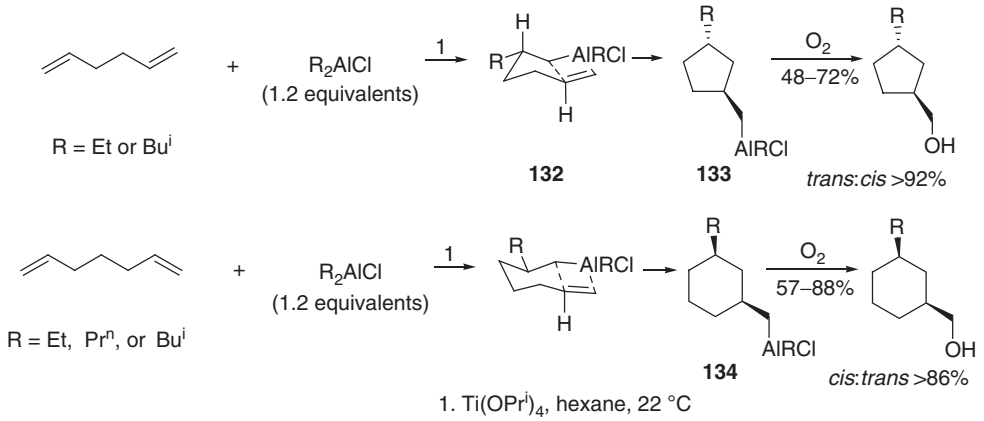
Scheme 87

The Ti-catalyzed carboalumination of 1,5-hexadiene or 1,6-heptadiene with dialkylaluminum chlorides affords cyclic organoaluminum species via an inter–intra cascade addition process (Scheme 88).[70] Their stereoselectivities are reverse to each other. For 1,5-hexadiene, the intermolecular carboalumination yields hex-5-enylaluminum intermediate **132** which undergoes subsequent intramolecular cyclic addition via chair cyclohexane-like transition state to yield the aluminated *trans*-1,3-disubstituted cyclopentanes **133**. The reaction of 1,6-heptadiene proceeds via the same process and transition state, giving the corresponding aluminated *cis*-1,3-disubstituted cycloheptanes **134**. The scope of this reaction is restricted to dialkylaluminum chlorides, other reagents such as trialkylalanes or alkylaluminum dichlorides are hardly reactive.

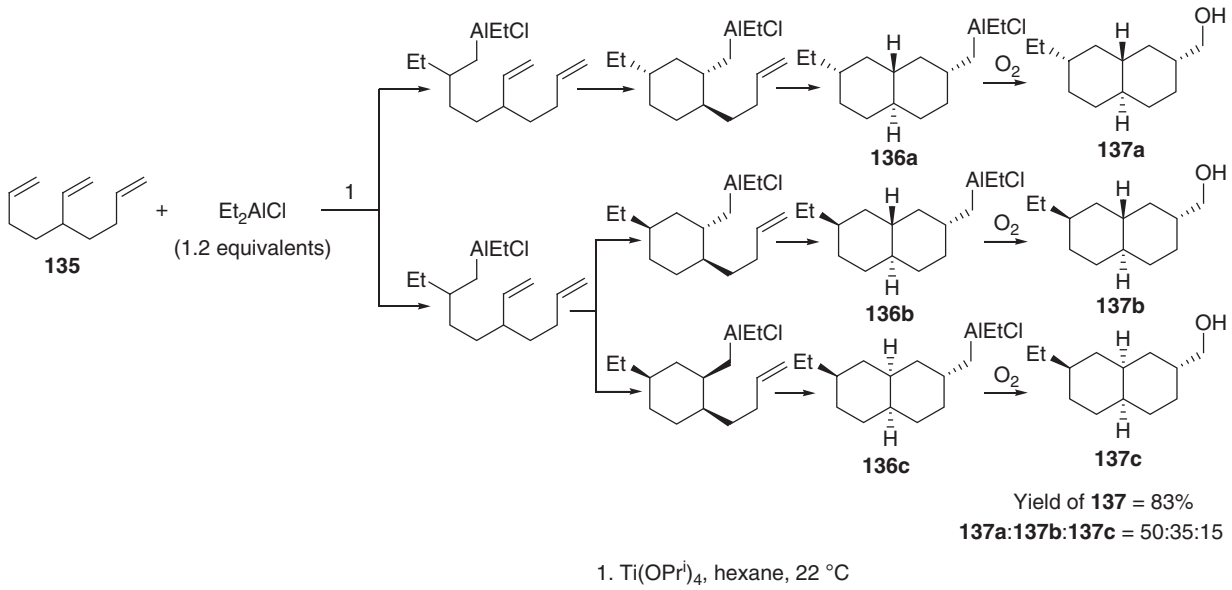
The reaction of triene **135** under identical conditions yields a mixture of bicyclic organoaluminum reagents **136a–c** via a similar inter–intra–intra cascade carboalumination process (Scheme 89).[70]

4.15.1.6.2 The carboalumination of alkynes

The Zr-catalyzed carboalumination of terminal alkynes reported first by Negishi in 1978[71] has been developed into a textbook method for the synthesis of trisubstituted alkenes, which has been applied as a crucial step in the total synthesis of a wide variety of natural products and related compounds of biological and medicinal importance.

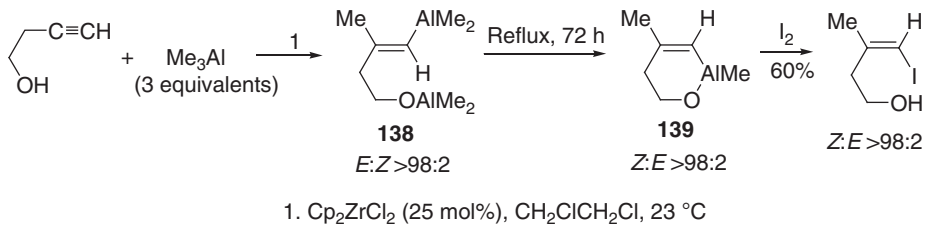


Scheme 88



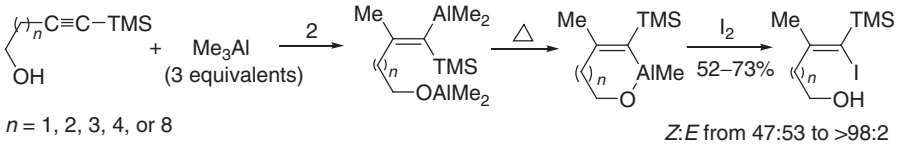
Scheme 89

Normally, this reaction undergoes a *syn*-addition process. However, in 1997, Negishi and coworkers reported the Zr-catalyzed *anti*-carboalumination of homopropargyl alcohols and some higher homologs via nonchelation-controlled *syn*-carboalumination and subsequent chelation-controlled isomerization (Schemes 90 and 91).[72] The treatment of 3-butyn-1-ol with 3 equivalents of Me_3Al in the presence of 25 mol% of Cp_2ZrCl_2 in CH_2ClCH_2Cl affords the normal *syn*-addition product **138** with a stereoselectivity of *E*:*Z* > 98:2.[73] In this step, no chelation occurs between the hydroxyl group and the aluminum atom. If this reaction mixture is allowed to stay at the refluxing temperature for an additional 72 h, the chelated six-membered aluminacycle **139** will be produced by the influence of the hydroxyl group and the stereoselectivity will change into *Z*:*E* > 98:2 (Scheme 90).



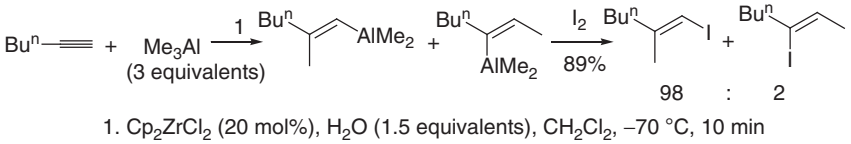
Scheme 90

After this isomerization, the *Z*-isomer turns to be the major product, which looks like a result from the *anti*-carboalumination reaction. Obviously, the hydroxyl group plays a key role in this reaction, since no *E*- to *Z*-isomerization occurs without the hydroxyl group. Substrates with substitution of the terminal hydrogen atom with $SiMe_3$ or $GeMe_3$ groups undergo the addition and isomerization smoothly, giving similar results. When higher homologs are applied, the selectivities drop along with the extension of the chain length. For 6-(trimethylsilyl)hex-5-yn-1-ol, the *anti*:*syn* ratio is 88:12. For 7-(trimethylsilyl)hept-6-yn-1-ol, the *anti*:*syn* ratio drops to 60:40. Further in case of 1-(trimethylsilyl)undec-10-yn-1-ol, the *anti*:*syn* ratio turns to be 47:53, in which the *syn*-adduct becomes the major one (Scheme 91).



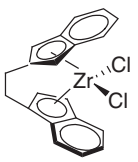
Scheme 91

In 1993, Wipf et al. found the addition of 1–2 equivalents of water could dramatically accelerate the reaction speed. Notably, in the presence of 1.5 equivalents of water, ever at −70 °C, the methylalumination of 1-hexyne completes within 10 min, affording a mixture of regioisomeric vinylalanes which can be converted into the corresponding vinyliodides by trapping with iodine. The aluminum atom is regioselectively transferred to the terminal position with an excellent ratio of 98:2 (Scheme 92).[74]



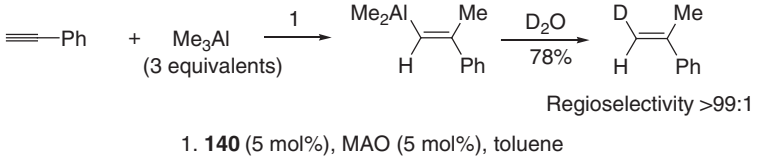
Scheme 92

By using bulky derivatives of Cp_2ZrCl_2 like rac-(ebi)$ZrCl_2$ **140** (Scheme 93) [75] as the catalyst and adding a catalytic amount of methyl aluminoxane, the regioselectivity can be improved to >99:1. The carbon–aluminum bond is only formed at the terminal position via a *cis*-addition process (Scheme 94).[75] Compared to the standard Negishi carboalumination, this reaction needs lower loading amounts of the catalyst, but leads to higher regiocontrol.



140

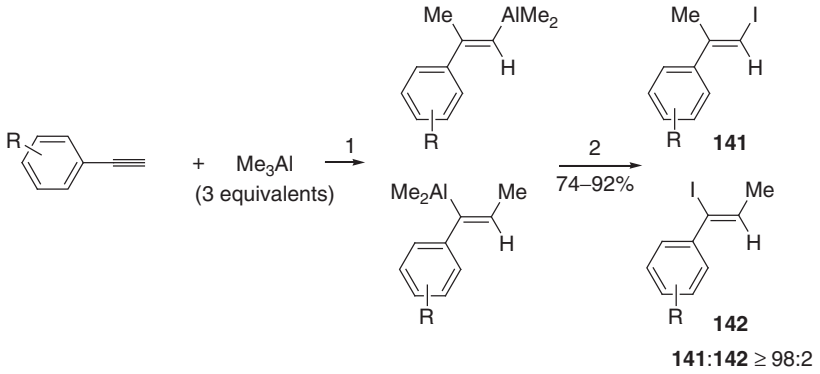
Scheme 93



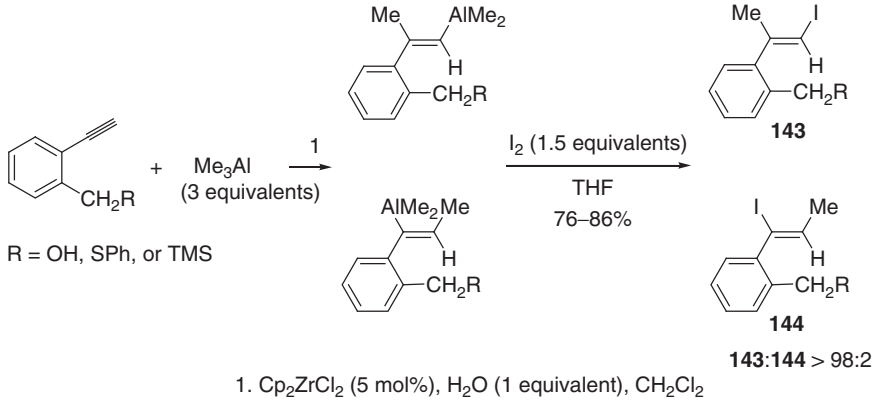
Scheme 94

This reaction is hardly affected by proximal heteroatoms such as O, S, Si, Cl, or Br. The organoaluminum adducts can be treated with a proper amount of I_2 to form the corresponding vinyl iodides. In all cases, the regioselectivities are as high as ≥98:2. For 2-hydroxyphenylethyne, 3-hydroxyphenylethyne, and 2-methoxyphenylethyne, less amounts of I_2 are required to achieve high

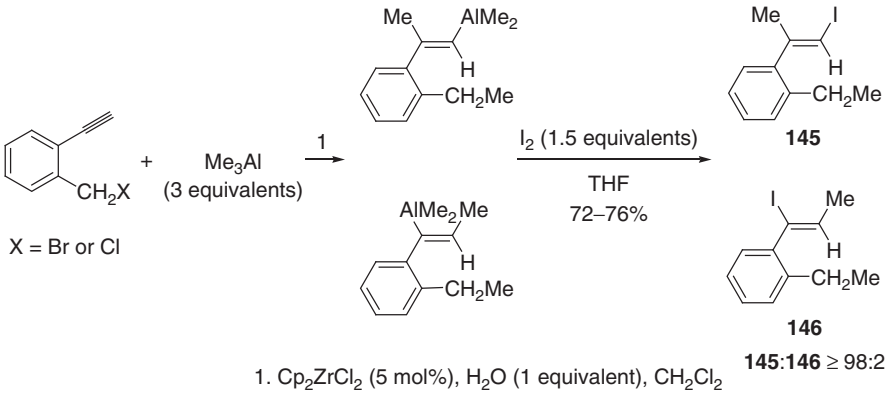
regioselectivities (Scheme 95).[76] The methylalumination of substrates like benzylically substituted heterofunctional group containing O, S, or Si also gives satisfying results. Both phenolic and benzylic hydroxyl groups can be readily accommodated without protection (Scheme 96).[76] If Br or Cl is introduced to the benzylic position, it will be replaced by a methyl group after nucleophilic attack during the reaction procedure (Scheme 97).[76]



Scheme 95



Scheme 96



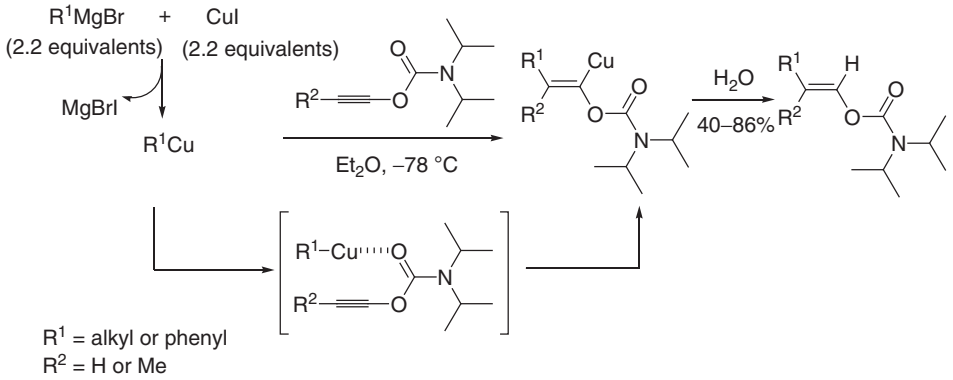
Scheme 97

4.15.1.7 The Carbocupration Reaction

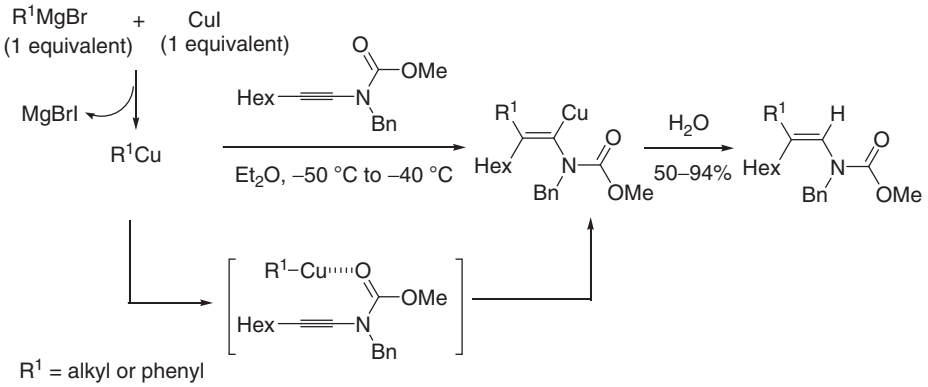
The carbocupration of alkenes or allenes is quite ineffective. No new achievements in this field were reported after 1990. In contrast, the carbocupration of alkynes occurs readily via absolute *syn*-process, affording alkenylcopper reagents with excellent regioselectivity. The formed organocoppers are synthetically useful and applied in many transformations.

4.15.1.7.1 The carbocupration of alkynes

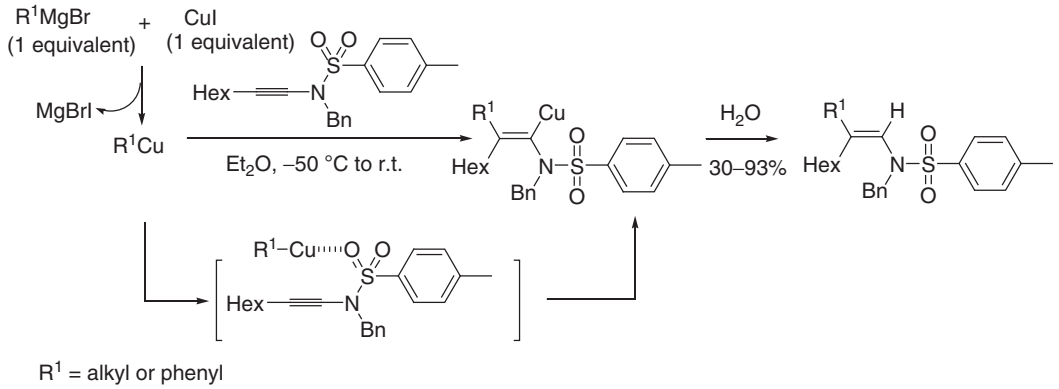
The organocopper species generated by the metal exchange of R^1MgBr with CuI undergoes carbocupration at low temperatures with alkynes bearing a heterofunctional group, affording alkenylcoppers as the only adduct. The chelation effect controls the regioselectivities, which leads to the results that the new formed carbon–copper bond is geminated to the heteroatom. Both terminal and internal alkynes are reactive. Primary and secondary alkylcoppers as well as phenylcopper can be used in this reaction (Schemes 98–100).[77]



Scheme 98

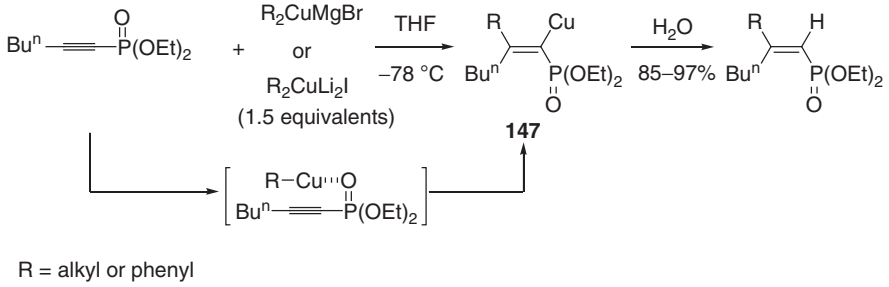


Scheme 99



Scheme 100

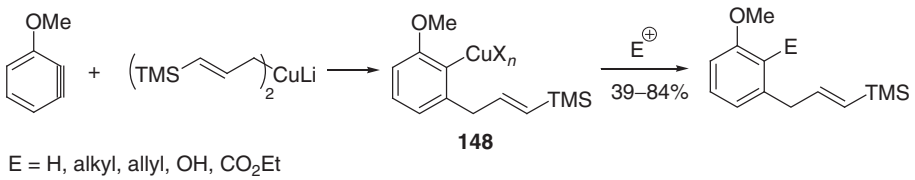
The addition of organocopper(I) reagents to alkynyl phosphonates affords vinylcopper(I) compounds **147**. The copper atom attacks at 1-position exclusively without any side products formed. The stereospecific *cis*-addition takes place in all cases. The chelation association and carbanion stabilization by the phosphonyl group may be the main reasons for the well-controlled selectivity. Terminal alkyne reactants also give high yields with perfect selectivities (Scheme 101).[78]



R = alkyl or phenyl

Scheme 101

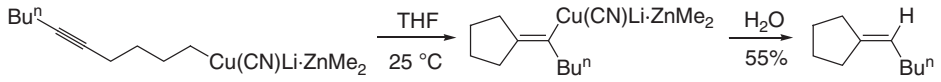
The addition to arynes proceeds smoothly, forming arylcuprates **148** which can be captured by a variety of electrophiles (Scheme 102).[79]



E = H, alkyl, allyl, OH, CO_2Et

Scheme 102

The intramolecular carbocupration of hex-5-ynyl copper-zinc organometallics **149** affords (cyclopentylidenemethyl)copper–zinc species **150** (Scheme 103).[80] This approach is limited to the five-membered ring system; attempts to construct four- or six-membered rings failed.

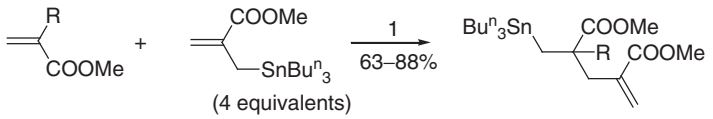


Scheme 103

4.15.1.8 The Carbostannylation Reaction

4.15.1.8.1 The carbostannylation of alkenes

Allyl stannanes bearing an electron-withdrawing group at the β-position can react with electron-deficient alkenes in the presence of azodiisobutyronitrile (AIBN), affording (pent-4-enyl)stannane derivatives via radical process. Mono- and 1,1-disubstituted alkenes such as methyl acrylate and methyl methacrylate give the addition products in good yields (Scheme 104).[81] Styrene and α-methylstyrene form quite low yields of the adducts. Dec-1-ene which only has a normal alkyl substituent does not show any

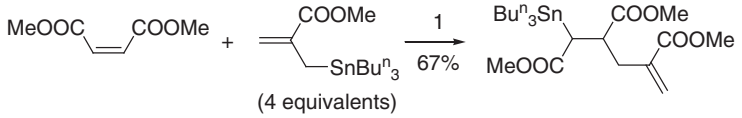


R = H or Me

1. AIBN (5 mol%), benzene, 80 °C

Scheme 104

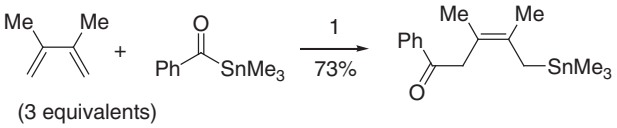
reactivity at all. For the reaction of 1,2-disubstituted alkenes, the two substituents must be both electron-withdrawing groups (equation 10),[81] otherwise, no reaction occurs.



(10)

1. AIBN (5 mol%), benzene, 80 °C

The Ni-catalyzed acylstannylation of 1,3-dienes yields allylstannanes in good yields. The acyl and trimethylstannyl groups are delivered to the 1,4-position of the dienes. This reaction provides a convenient method for the synthesis of allylstannanes having a carbonyl group (equation 11).[82]



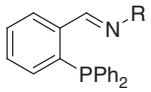
(11)

1. Ni(COD)$_2$ (5 mol%), toluene, 50 °C

4.15.1.8.2 The carbostannylation of alkynes

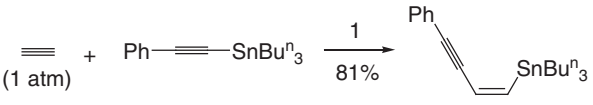
The carbostannylation of alkynes is of high preparative value, since vinyllic stannanes which undergo diverse transformations and are widely applied in organic synthesis can be easily prepared by this method. Under the catalysis of transition metals, such as palladium,[83–85] nickel,[86] and zirconium,[87] this reaction takes place in high yield. Although a mixture of regioisomers may be formed in some cases, the stannanyl group attaching to the electron-rich position of the alkyne moiety is highly preferred. In AIBN-initiated radical reactions,[88] *trans*-selectivity is preferred. The scope of this reaction is broad. Acetylene, terminal and internal alkynes, as well as various organic tin reagents are all tolerant.

Under the catalysis of iminophosphine **151** (Scheme 105)[83] palladium complex, the carbostannylation of alkynes with alkynylstannanes affords enynylstannanes. Under an acetylene atmosphere (1 atm), the reaction of tributyl(2-phenylethynyl) stannane forms tributyl[(*Z*)-2-(phenylethynyl)ethenyl]tin as a single isomer through an exclusive *syn*-addition (equation 12).[83]



151a: R = $(CH_2)_2Ph$
151b: R = Cy
151c: R = Bu^t
151d: R = CH_2CMe_3
151e: R = Ph

Scheme 105

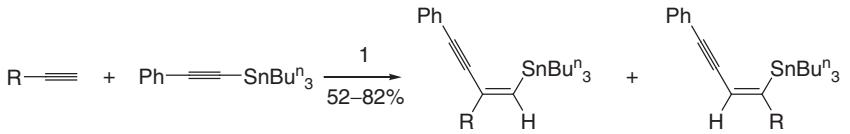


(12)

1. [PdCl(η^3-C_3H_5)]$_2$ (2.5 mol%), **151a** (5 mol%), THF, 50 °C

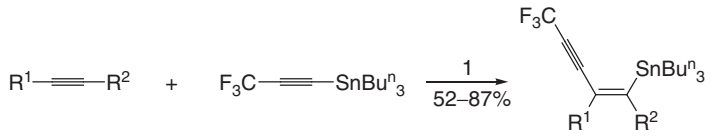
This catalyzed addition to other alkynes leads to a mixture of regioisomers in some cases, however, no *trans*-isomers are formed. The regioselectivity is fully reactant dependent. The tributylstannanyl group is selectively attached to the electron-rich carbon atom of the carbon–carbon triple bond. Steric bulk of ligand **151** shows great influence on the regioselectivity and reaction speed rate: with a bulkier imino moiety, the addition is accelerated with higher regioselectivity (Scheme 106).[83]

Tributyl (3,3,3-trifluoropropynyl)stannane shows higher reactivity in the Pd-catalyzed carbostannylation of alkynes. This reaction proceeds smoothly at room temperature, producing the single stereospecific CF_3-substituted enynylstannane via the *syn*-addition process. The new carbon–stannum bond is exclusively formed at the electron-rich position of the alkyne moiety (Scheme 107).[84]



1. [PdCl(η^3-C_3H_5)]$_2$ (2.5 mol%), **151** (5 mol%), THF, 50 °C

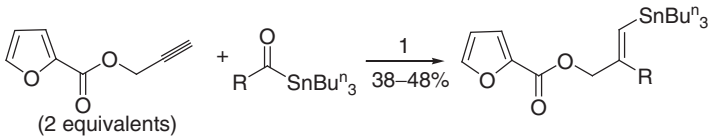
Scheme 106



1. Pd2(dba)$_3$ (1 mol%), Bu$^t_3$P (2 mol%), toluene, r.t.

Scheme 107

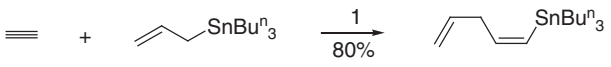
At a very low loading amount of the palladium catalyst (0.2 mol% on Pd), both $Pd_2(dba)_3$ and Pd/C can catalyze the decarbonylative carbostannylation of acylstannanes to alkynes, however, the yields are low (Scheme 108).[85] The Bu^n_3Sn group is attached to the terminal position of the alkyne moiety via *syn*-addition process without any regio- or stereoisomers formed. The formal alkyl-, alkenyl-, and arylstannylations can be easily achieved by using the corresponding acylstannanes.



1. $Pd_2(dba)_3$ (0.1 mol%) or Pd/C (0.2 mol% Pd), Bu_2O, 50 °C

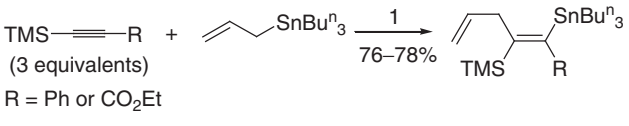
Scheme 108

Ni(0) can also catalyze the allyl-, acyl-, and alkynylstannylations of alkynes with *syn*-selectivity. Treatment of acetylene with allyl(tributyl)tin under the catalysis of $Ni(COD)_2$ affords (*Z*)-tributyl(penta-1,4-dienyl)stannane in good yield (equation 13).[86] The reaction of phenylacetylene or ethyl propiolate leads to only the self-polymerization products. In contrast, the addition to internal alkynes produces the desired alkenylstannanes, irrespective of electron-withdrawing or -donating character of the substituent of the alkyne. In most cases, only one regioisomer is formed when unsymmetrical internal alkynes are applied (Scheme 109).[86] Notably, no allylic rearrangement takes place in the reaction of crotylin with 1-phenyl-1-propyne (equation 14).[86]



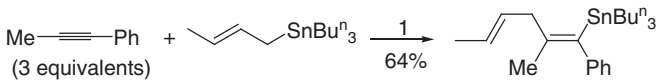
(13)

1. $Ni(COD)_2$ (5 mol%), toluene, 80–100 °C



1. $Ni(COD)_2$ (5 mol%), toluene, 80–100 °C

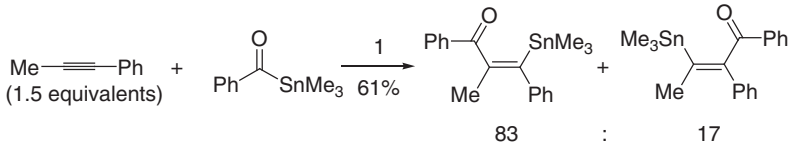
Scheme 109



(14)

1. $Ni(COD)_2$ (5 mol%), toluene, 80–100 °C

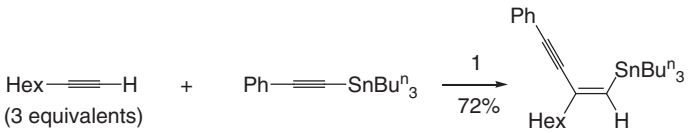
The Ni-catalyzed acylstannylation of unsymmetrical internal alkynes results in a mixture of regioisomers (equation 15).[86]



(15)

1. $Ni(COD)_2$ (5 mol%), toluene, 100 °C

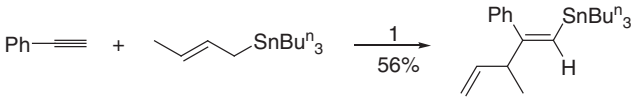
The *in situ* generated Ni(0) catalyst from the reaction of $Ni(acac)_2$ with Bu^i_2AlH, is more effective than $Ni(COD)_2$ for the alkynylstannylation. The addition with terminal alkynes affords enynylstannanes with perfect regio- and stereoselectivities (equation 16).[86] This is in sharp contrast to the Pd-catalyzed alkynylstannylation which forms a mixture of regioisomers (**Scheme 106**).[83] This reaction is limited to the electron-rich terminal alkynes. Other alkynes are not suitable.



(16)

1. $Ni(acac)_2$ (5 mol%), Bu^i_2AlH (10 mol%), toluene, 80 °C

Treatment of terminal alkynes with allyl(tributyl)stannanes using 20 mol% of $ZrCl_4$ as the Lewis acid catalyst, affords penta-1,4-dienyl(tributyl)stannane derivatives **152**. An allylic rearrangement is observed in the reaction of crotylstannane (equation 17).[87] Enynes are more reactive than arylacetylenes. Simple alkylacetylene is very unreactive, giving a very low yield of the allylstannylation product. In all cases, only one single product is formed with the stannyl group attached to the terminal position of the alkyne moiety via the *trans*-addition process.

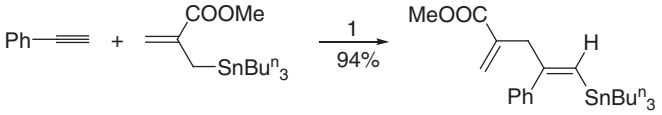


152

(17)

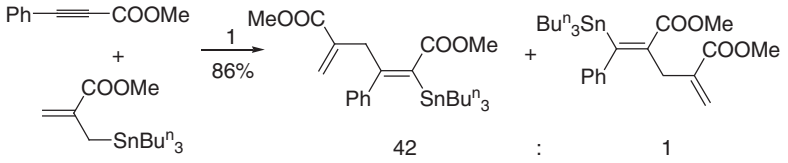
1. $ZrCl_4$ (20 mol%), toluene, −78 °C to 0 °C

The AIBN-initiated allylstannylation of alkynes also proceeds *trans*-selectively via a radical process. The introduction of an electron-withdrawing group at the *β*-position of the allylstannane reagents significantly improves the reactivity. The addition to terminal alkynes shows perfect regio- and stereoselectivities in most cases (equation 18).[88] However, the alkylsubstituted simple acetylenes give quite low yields. Internal alkynes without an electron-withdrawing group substituent are very inreactive. While the reaction of alkynes with electron-withdrawing groups affords a mixture of regioisomers. The major product is the isomer with the stannyl group attached to the electron-rich position (equation 19).[88]



(18)

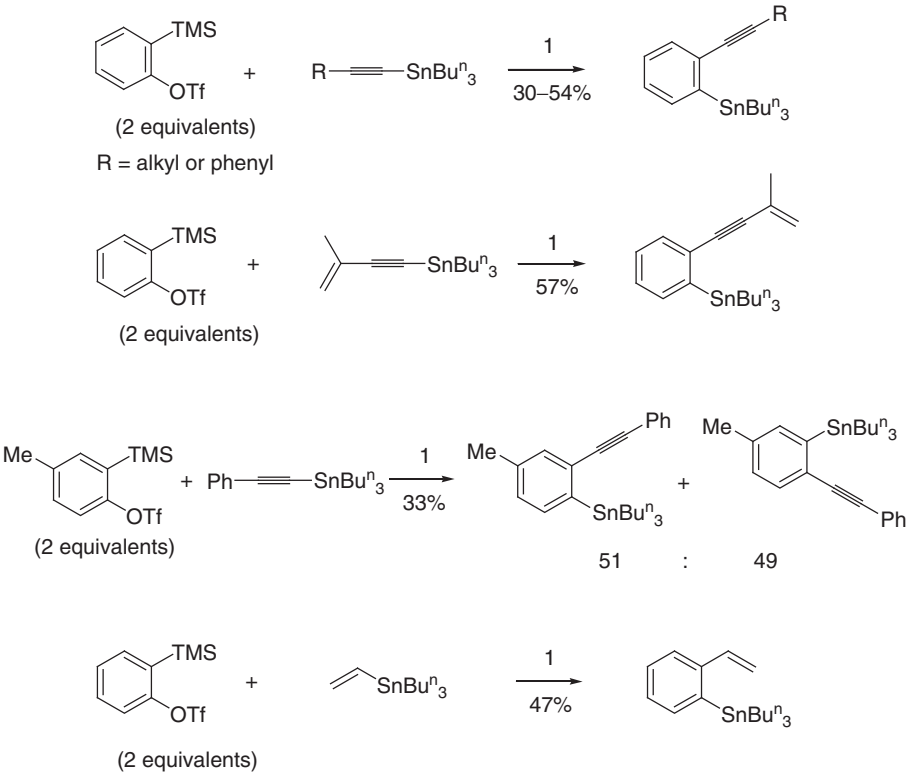
1. AIBN (5 mol%), benzene, 80 °C



(19)

1. AIBN (5 mol%), benzene, 80 °C

The alkynylstannylation of benzyne can be realized by the catalysis of palladium–iminophosphine **151** complex. This is a convenient method for the synthesis of *ortho*-substituted arylstannanes (Scheme 110).[89] Both alkyl- and phenylethynyltins can add to the *in situ* prepared benzynes. Conjugated enynylstannanes also react smoothly to form the corresponding organostannanes. The carbostannylation of substituted arynes leads to a mixture of two regioisomers with the ratio of approximately 1:1. Notably, tributyl(2-vinylphenyl)stannane is formed in 47% yield by the catalytic addition of benzyne with tributyl(vinyl)tin which shows no reactivity toward alkynes under similar condition.[83]



1. CsF (2 equivalents), $[Pd_2Cl_2(\eta^3\text{-}C_3H_5)_2]$ (2.5 mol%), **151** (5 mol%), MeCN, 50 °C

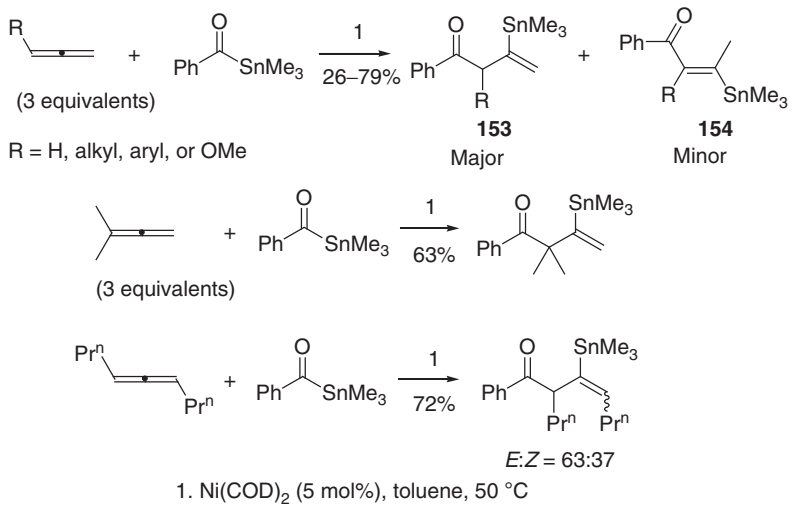
Scheme 110

4.15.1.8.3 The carbostannylation of allenes

$Ni(COD)_2$ is found to be an effective catalyst for the carbostannylation of allenes.[90,91] Normally, a mixture of regio- or stereoisomers are formed in this reaction. However, the tin atom is exclusively attached to the middle carbon of the allene moiety.

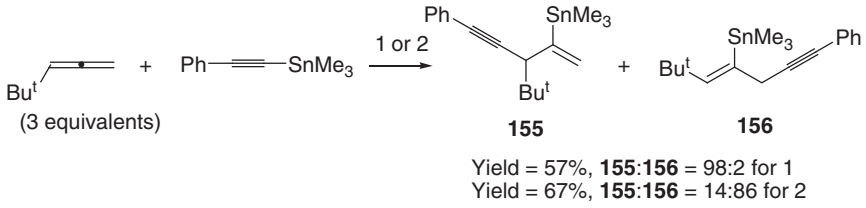
The acylstannylation of allenes affords α-(acylmethyl)vinylstannanes in good yields (Scheme 111).[90] This addition occurs at the internal carbon–carbon double bond. In some cases, a small amount of the decarbonylated products are formed. The reaction of non- or monosubstituted allenes results in organostannum species **153** and a minimum amount of **154** which may derive through the isomerization of **153**. The 1,1- or 1,3-disubstituted allenes also participate in this acylstannylation, yielding the corresponding adducts.

The alkynylstannylation of monosubstituted allenes leads to a mixture of regioisomers **155** and **156**. The ligand effect plays a crucial role in this reaction. Only bidentate biphosphine ligands which chelate with the nickel atom to form a six-membered ring system can accelerate this addition. Ligands that form five- or seven-membered chelates show no catalysis at all. Notably, using 1,3-bis(dimethylphosphino)propane (dmpp) as the ligand leads to the reversed regioselectivity as that of 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 112).[90b] The scope of this reaction is quite broad. Non-, mono-, 1,1-, and 1,3-disubstituted



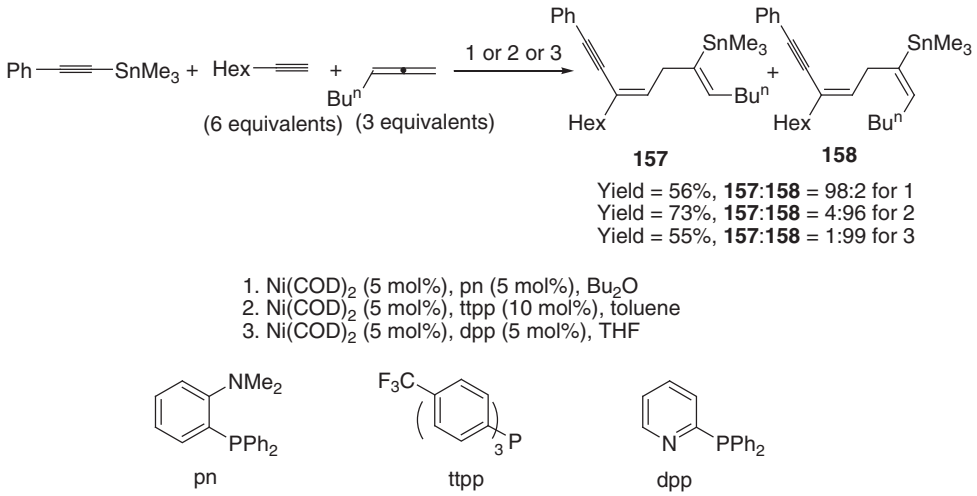
Scheme 111

allenes are all reactive with various alkynylstannanes. In all cases, the stannyl group is regiospecifically introduced to the middle carbon of the allene moiety.



Scheme 112

An Ni-catalyzed tandem carbostannylation of alkynes and allenes with alkynylstannanes proceeds through *syn*-alkynylstannylation of alkynes and subsequent alkenylstannylation of allenes, affording vinyltin complexes **157** and **158** (Scheme 113).[91] Three standard conditions were established using 5 mol% of $Ni(COD)_2$ as the catalyst and (2-(dimethylamino)phenyl)diphenylphosphane (5 mol%) in Bu_2O for Conditions A, tri(*p*-(trifluoromethyl)phenyl)phosphane (10 mol%) in toluene for Conditions B, and 2-(diphenylphosphanyl)pyridine (5 mol%) in THF for Conditions C. It is worthy to note that the selectivities are so



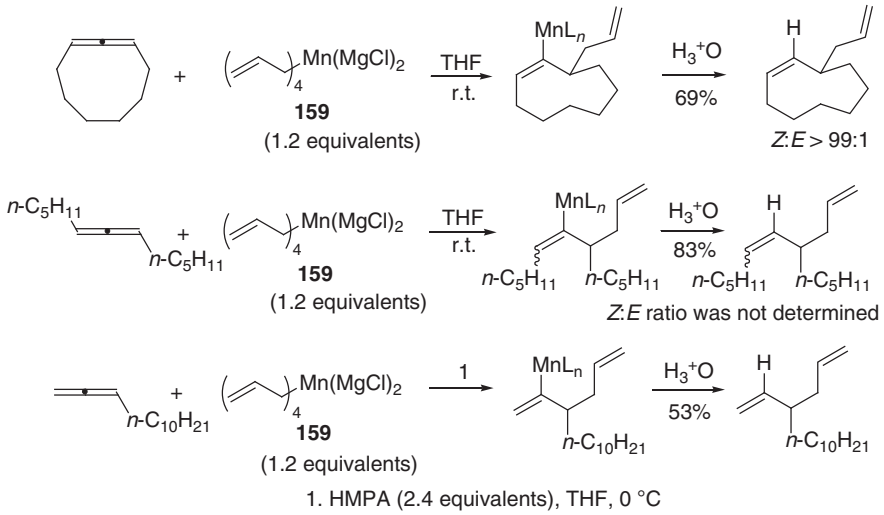
Scheme 113

well controlled that only two stereoisomers are formed out of the 48 possible isomers. Furthermore, sharply reversed selectivities can be easily achieved by applying Conditions A or Conditions B or Conditions C. However, this reaction is restrained to terminal alkynes and monosubstituted allenes. Only very poor yields are obtained with internal alkynes or 1,1-disubstituted allenes.

4.15.1.9 The Carbomanganation Reaction

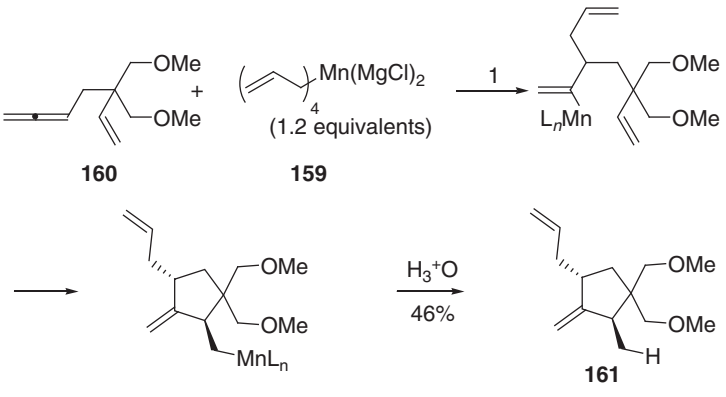
4.15.1.9.1 The carbomanganation of allenes

Treatment of allenes with tetraallylmanganate **159**, prepared from the reaction of allylmagnesium chloride and manganese(II) chloride in a 4:1 ratio, affords alkenylmanganese(II) species as the carbomanganation product. The manganese atom is regiospecifically attached to the middle carbon atom of the allene moiety. Both internal and terminal allenes are suitable for this reaction, however, 2.4 equivalents of HMPA is required for the reaction of terminal allenes, otherwise, the yields are very low (Scheme 114).[52]



Scheme 114

Under identical conditions, the diastereoselective cyclization of 1,2,6-heptatriene derivative **160** forms the five-membered ring product **161** via inter–intramolecular carbomanganation and subsequent aqueous workup (Scheme 115).[52]



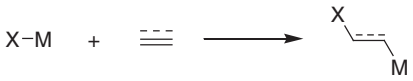
Scheme 115

4.15.2 Heterometalation of Alkenes, Alkynes, and Allenes

4.15.2.1 Introduction

The addition of a hetero–metal bond of an organometallic compound to a carbon–carbon multiple bond is of great interest because a new carbon–hetero atom bond as well as a new carbon–metal bond are formed just in a single step, also, the new

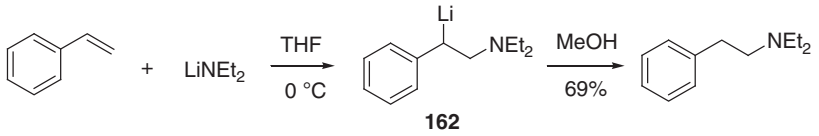
formed carbon–metal bond can serve as an active metal functional group in further transformations. Normally, this type of reaction is called heterometalation (equation 20). Heterometalation is not studied as extensively as carbometalation, until now, there are only a few results reported in this field. To briefly introduce this type of reactions, herein, the aminolithiation, aminocupration, oxymercuration, and thioboration are addressed.



(20)

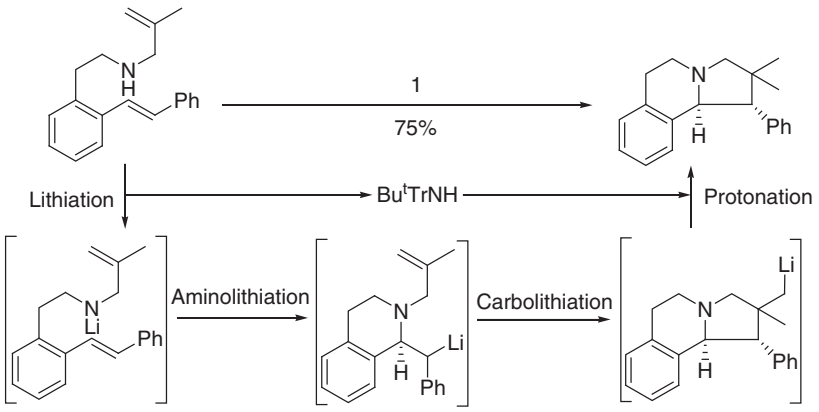
4.15.2.2 The Aminolithiation Reaction

Normally, the reactions of styrenes with lithium or sodium amides only result in the formation of polystyrenes through anionic polymerization. In 1998, Seijas and Vázquez-Tato et al. reported the aminolithiation of lithium amides, generated by the hydrogen–lithium exchange of amines with Bu^nLi, to styrene and its derivatives, regioselectively affording the benzylic lithium species **162** which can be quenched by MeOH to produce *β*-phenylethylamines (Scheme 116).[92]



Scheme 116

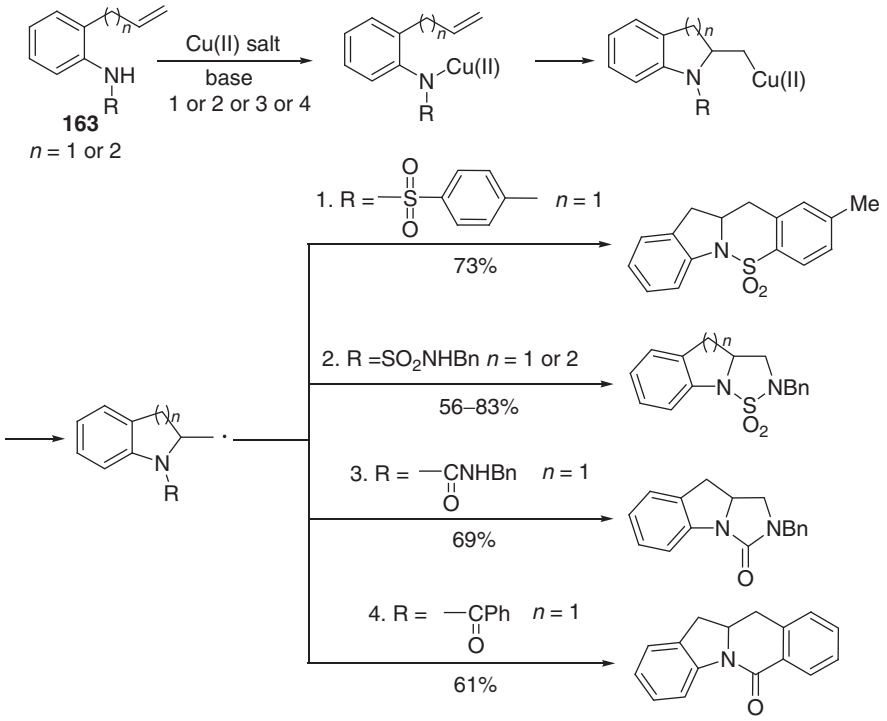
A Bu^tTrNLi involving consecutive intramolecular aminolithiation of allylaminoalkenes affords bicyclic amines in good to excellent yields with high diastereoselectivities via tandem lithiation–aminolithiation–carbolithiation–protonation process. Bu^tTrNLi is used as the lithiating reagent to start this reaction at the first step, then the resulting Bu^tTrNH will act as the protonating agent to quench the lithium intermediate which results in the formation of the final product at the last step (Scheme 117).[93]



Scheme 117

4.15.2.3 The Aminocupration Reaction

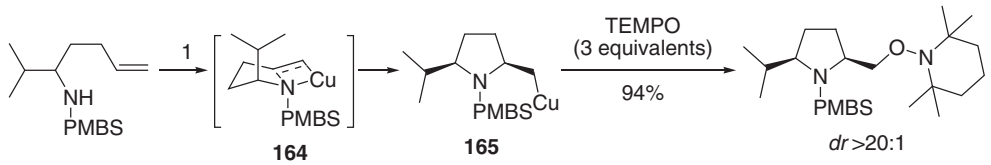
The intramolecular aminocupration of *o*-allyl- or *o*-homoallylaniline derivatives **163** having an electron-withdrawing group such as carbonyl or sulfonyl on the nitrogen atom, generated by hydrogen–copper exchange of the corresponding anilines and copper(II) salts in the presence of an excess amount of base, affords 2-(coppersubstituted methyl) indoline or 1,2,3,4-tetrahydroquinoline derivatives. These organocopper complexes undergo several intramolecular radical cyclizations, forming multicyclic systems (Scheme 118).[94]



1. $Cu(OAc)_2$ (3 equivalents), Cs_2CO_3 (1 equivalent), DMF, CH_3CN, 120 °C
2. $Cu(OAc)_2$ (3 equivalents), K_2CO_3 (2 equivalents), DMF, DMSO, 90 °C
3. $Cu(ND)_2$ (3 equivalents), K_2CO_3 (2 equivalents), DCE, 120 °C
4. $Cu(EH)_2$ (3 equivalents), Cs_2CO_3 (1 equivalent), DMF, 190 °C

Scheme 118

The treatment of 2-methylhept-6-en-3-amine derivates with 3 equivalents of copper(II) salt and 2 equivalents of base affords the aminocopper intermediates **164** which further undergo the aminocupration reaction with the intramolecular terminal carbon–carbon double bond to yield the *cis*-2,5-disubstitutedpyrrolidine organocopper derivatives **165** with a dr value of >20:1 (Scheme 119).[95]



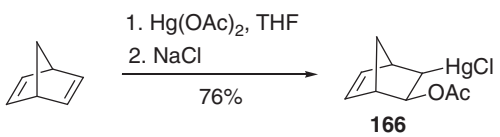
PMBS = *para*-methoxybenzenesulfonyl

1. $Cu(eh)_2$ (1.5 equivalents), $CsCO_3$ (2 equivalents), xylene, 130 °C

Scheme 119

4.15.2.4 The Oxymercuration Reaction

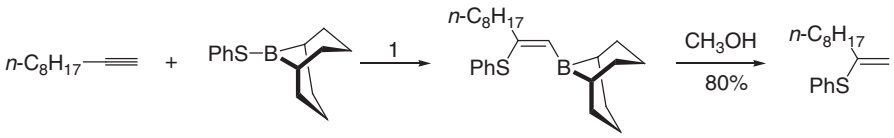
The *syn*-oxymercuration of norbornadiene or 2-substituted norbornenes gives oxymercurial compounds **166** in good to excellent isolated yields after chromatography. This reaction proceeds in several nonaprotic solvents, among which THF provides the highest yield and selectivity (Scheme 120).[96]



Scheme 120

4.15.2.5 The Thioboration Reaction

Thioboration reaction is not studied as well as hydroboration, haloboration, and diboration reactions, since the heteroboration usually does not take place due to the high heteroatom–boron bond energy and the low Lewis acidities of borons conjugated to heteroatoms. Until now, only Suzuki and Miyaura et al. reported the thioboration of terminal alkynes with 9-(alkylthio)-9-borabicyclo[3.3.1]nonane derivatives (9-(RS)-9-BBN) catalyzed by $Pd(PPh_3)_4$ (**Scheme 121**).[97] The boron atom is regioselectively introduced to the terminal position of the alkyne through the *syn*-addition process, yielding *Z*-alkenylborons which can be readily transformed into vinyl sulfides after protonolysis. Higher yields can be generated by adding 1 equivalent of styrene into the reaction mixture. Generally, no difference is observed between the reaction of (alkylthio)- and (arylthio)boranes, except for the very sterically hindered (*tert*-butylthio)borane derivative. This reaction only works with terminal alkynes so that the resulting double bonds remained intact. Notably, the reaction conditions are sufficiently mild to tolerate acetal, nitrile, and carbonyl groups. However, it is rather sensitive to the steric hindrance of alkynes. Only a very low yield can be obtained when cyclohexylethyne is applied.



1. $Pd(PPh_3)_4$ (3 mol%), styrene (1 equivalent), THF, 50 °C

Scheme 121

4.15.3 Conclusion

Carbometalation has been extensively explored in the last few decades. The high efficiency in constructing a synthetically useful organometallic intermediate has made this reaction to be widely applied in organic chemistry. A series of transition metal catalysts have been proven to be efficient, leading to high selectivity controls in good to excellent yields. However, in some cases, the reaction is still not efficient enough, affording a mixture of products in low yields. How to improve the reactivities and selectivities in such cases is obviously an important task in this field.

Heterometalation is also an important reaction, since the resultant active metal functional group can serve in further transformations. However, this reaction is not investigated as well as carbometalation with only a few achievements reported. This limitation prevents heterometalation from playing an even more important role in synthetic chemistry. Thus, further studies in this field and development of new reactions are highly desired.

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4.16 Bismetallation and Bismetallative Reaction of Alkenes, Alkynes, and Allenes

JP Morken, Boston College, Boston, MA, USA

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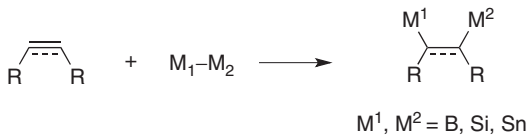
4.16.1 Introduction

Since the early 1990s, bismetallation of unsaturated hydrocarbons has continued to gain prominence in catalysis and organic synthesis.[1] These advances have been enabled by the introduction of effective bismetallation catalysts, an enhanced understanding of their catalytic reaction mechanisms, and the introduction of selective chiral catalysts that enable application to contemporary asymmetric synthesis. Recent research has resulted in the discovery of metal-free catalytic systems for the bismetallation of unsaturated hydrocarbons, and this promises to have a more pronounced impact in the future. This overview of bismetallation will focus exclusively on its application to unactivated hydrocarbon substrates (alkenes, alkynes, and allenes) wherein two metals are added to the substrate of interest. Important advances in conjugate boron additions and allylic substitutions are outside the scope of this survey.[2] Almost exclusively, bismetallation is accomplished by the reaction of a metal–metal-bonded reagent to the substrate (Scheme 1); thus, the few reactions that proceed under noncatalytic reaction conditions are not covered in this chapter.[3]

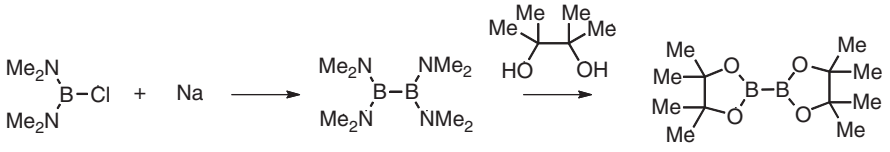


Scheme 1

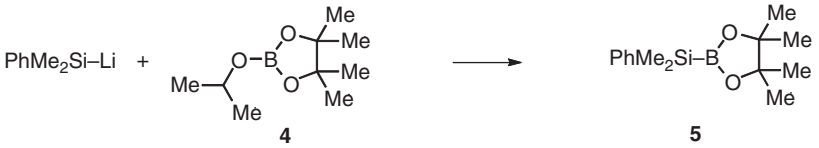
4.16.1.1 Reagent Preparation

One significant feature that has facilitated the development of catalytic bismetallation reactions is the introduction of effective methods for reagent preparation. Indeed, a number of the reagents covered in this chapter are now commercially available on

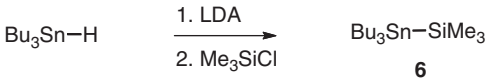
commodity chemical scales. The synthesis sequences depicted in equations 1–3 are representative of the routes that can be used for the production of specialized derivatives, and they have proven to be highly reliable strategies. Diboron reagents are most conveniently prepared by Wurtz-type coupling of diaminochloroborane **1** to give **2**.[4] Although the nitrogen donors on **2** generally deactivate the reagent for bismetallation reactions, addition of alcohols converts **2** to more reactive bis(boronic)esters such as **3** (equation 1). Silylboron reagents are most conveniently prepared by the generation of a silyllithium followed by an electrophilic trap with borate **4** (equation 2).[5] An effective strategy for the construction of silylstannanes arises from deprotonation of a triorganostannane followed by trapping with a silyl chloride (equation 3).[6]



(1)



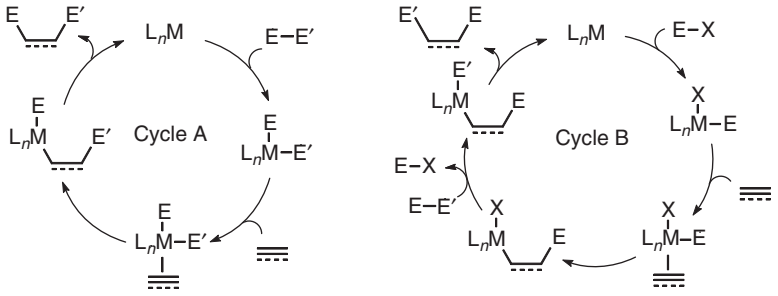
(2)



(3)

4.16.1.2 General Catalytic Mechanisms

With some variation, two general reaction mechanisms operate for most catalytic bismetallation reactions.[7] One mechanism is depicted in cycle A of Scheme 2, where oxidative addition of the transition metal catalyst with a metal–metal-bonded reagent (E–E′) is the first step.[8] According to calculations involving boron-based reagents, a requisite step is association of the reagent with the catalyst by a metal d electron donation to the empty orbital on boron.[9] The importance of this interaction can explain the diminished reactivity of tetrakis(dimethylamino)diboron (**2**; equation 1) in diboration reactions; electron donation from nitrogen to boron in **2** renders this reagent less able to interact with the transition metal catalyst. On completion of cycle A, substrate coordination and insertion are followed by reductive elimination that releases the product and returns the catalyst to the original oxidation state. Cycle B also accomplishes bismetallation but does so without requiring oxidative addition with the metal–metal, bonded reagent. As has been determined for a palladium-catalyzed allene diboration, cycle B can be initiated by oxidative addition of the catalyst to a metal halide (E–X).[10] Substrate insertion is followed by transmetallation with the metal–metal-bonded reagent. This step regenerates the metal halide and provides an intermediate poised for product release.



Scheme 2

The above-mentioned cycles suggest that bidentate ligands should inhibit the reactions when group 10 metals are used: In these cases, the metal complex would have a d^8 electron count after oxidative addition, and the four-coordinate square planar complex would be unable to coordinate an alkene substrate. Alternatively, group 9 complexes that originate catalysis from the +1 oxidation state have a d^6 electron count after oxidative addition and, even in the presence of a bidentate ligand, there is still an open coordination site for substrate association.

In addition to the catalyst, the nature of the bismetallation reagent is an important consideration. Studies that examine the impact of silylboron on reactivity are not prevalent; however, a number of reports have examined the structural effects of disilane and diboron reagents. Generally, the rate of the catalytic disilylation increases as the electronegative groups are attached to silicon.[11] Qualitative observations by Marder suggest that the oxidative addition of the diboron reagent $B_2(cat)_2$ to $(Ph_3P)_2Pt(ethylene)$ is faster than the same reaction with $B_2(pin)_2$. This observation is unexpected, given the fact that the B–B bond length of $B_2(cat)_2$ (1.68 Å) is shorter than that of $B_2(pin)_2$ (1.71 Å).[8c] Studies by Smith indicate that the bis(boryl) species derived from oxidative addition of $B_2(cat)_2$ to Pt(0) may be more stable than those derived from $B_2(pin)_2$.[12] (More precisely, the equilibrium $B_2(cat)_2 + (Ph_3P)_2Pt(Bpin)_2 \rightleftarrows B_2(pin)_2 + (Ph_3P)_2Pt(Bcat)_2$ lies all the way to the right). However, in the absence of thermochemical data for $B_2(cat)_2$, the stability of the Pt complexes discussed above is not rigorously established. Collectively, these studies provide a framework to understand the diminished reactivity of $B_2(pin)_2$ relative to $B_2(cat)_2$ in catalytic diboration. These observations also provide insight into the observation that Pt(0) complexes are generally more effective in diboration than Rh(I) and Pd(0) – the increased d-electron energy of Pt(0) facilitates oxidative addition relative to Pd(0) and Rh(I).

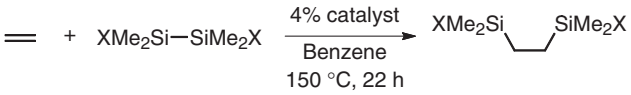
4.16.2 Bismetallation of Alkenes

4.16.2.1 Disilylation of Alkenes

4.16.2.1.1 Intermolecular disilylation of alkenes

Tanaka documented the first example of catalytic bismetallation of simple alkenes, specifically ethylene and norbornene.[13] Several features of this reaction are common to bismetallations and are worthy of note: First, the reaction was most effective with Pt catalysts, with Pd, Ru, and Rh complexes being inactive (compare entries 4 and 5, Table 1); second, reactivity is enhanced in the presence of Lewis basic nonhindered phosphines (entry 2 vs. 4); third, the reaction was most efficient with electron-withdrawing and less encumbered groups attached to the disilicon reagent (compare entries 1–3). Lastly, the reaction conditions, and the observation that the disilylation of norbornene occurs in a *syn* fashion, suggest that this transformation likely occurs by cycle A.

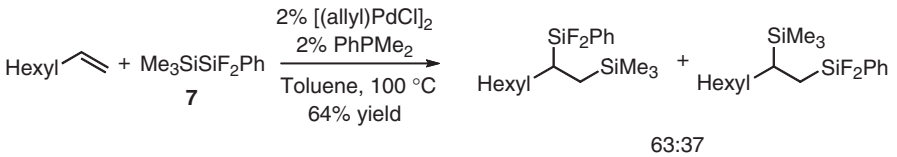
Table 1 Disilylation of ethylene



Entry	*Catalyst*	*X*	*% Yield*[a]
1	$Pt(PPh_3)_4$	Me	18
2	$Pt(PPh_3)_4$	Ph	4
3	$Pt(PPh_3)_4$	F	95
4	$Pt(PPhMe_2)_4$	Ph	30
5	$Pd(PPh_3)_4$	Ph	No reaction

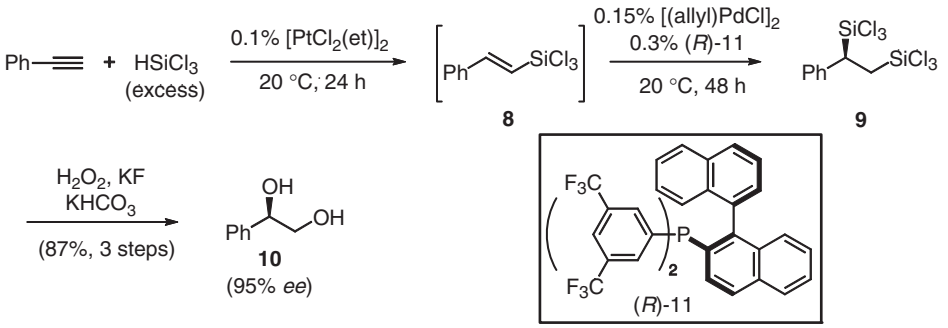
[a]GC yield based on $XMe_2Si–SiMe_2X$ as the limiting reagent.

Hayashi examined the disilylation of simple α-olefins and alkynes under the influence of Pd catalysts and the accompanying mechanistic studies merit mention.[14] As depicted in equation 4, 1-octene undergoes catalytic disilylation with nonsymmetric disilane **7** with moderate regioselectivity. There are two important observations in this study: The reaction with styrene provided the opposite product regioisomer (28:78 ratio) and there was no reaction when $Me_3SiSiMe_3$ or PhF_2SiSiF_2Ph was used in place of **7**. In connection to the latter finding, it is revealing that in stoichiometric experiments both **7** and PhF_2SiSiF_2Ph were found to undergo oxidative addition with $(Ph_2MeP)_2Pd(styrene)$ complex furnishing $(Ph_2MeP)_2Pd(SiR_3)_2$. Notably, the use of less electron-rich catalysts revealed that the oxidative addition appears to be more favorable with PhF_2SiSiF_2Ph relative to **7**. Collectively, these studies suggest that though electron-deficient disilanes are required for oxidative addition, if they are too electron deficient, the stability of the oxidative addition adduct may preclude subsequent steps in the catalytic cycle.



(4)

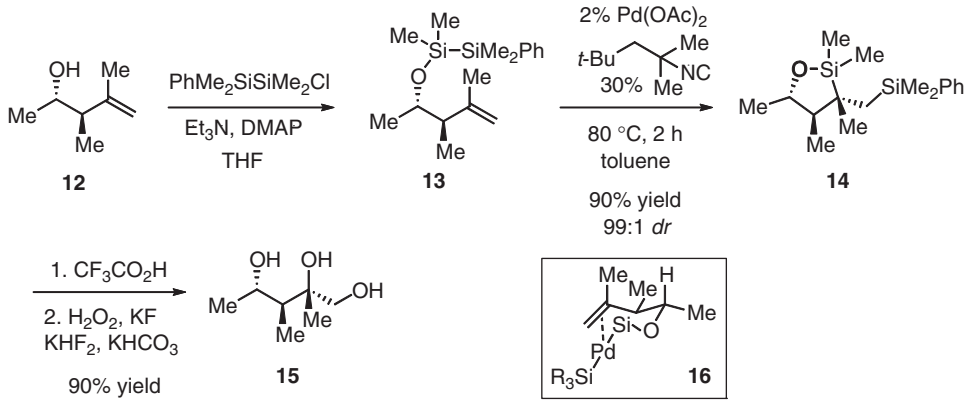
Although highly enantioselective disilylation of simple alkenes has not been demonstrated, nonracemic 1,2-disilicon species have been obtained by the reaction of alkyne substrates. As indicated in Scheme 3, the double hydrosilylation of phenylacetylene occurs to give **9** via intermediate vinylsilane **8**.[15] Importantly, two different catalysts are used for this reaction, with a Pt complex in the first step and a Pd complex in the second. Because the Pt complex is ineffective for the second step, the entire sequence can be accomplished in one reaction vessel, with the Pd catalyst added after the first transformation has reached completion. Subjection of **9** to Tamao oxidation furnished the enantiomerically enriched 1,2-diol **10** in excellent isomeric purity.



Scheme 3

4.16.2.1.2 Intramolecular disilylation of alkenes

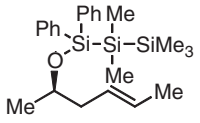
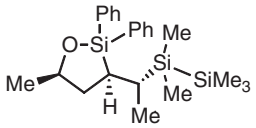
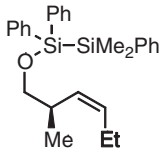
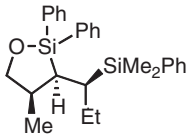
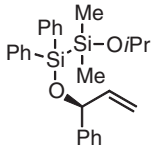
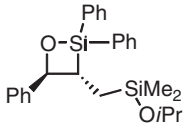
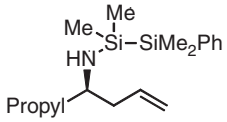
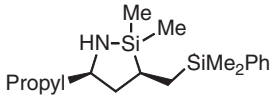
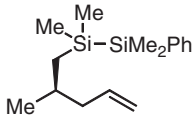
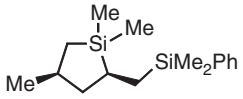
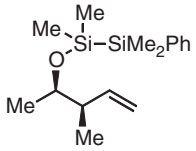
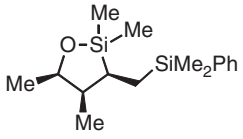
Disilylation of internal alkenes is more challenging than the terminal alkenes described above. In one intriguing example, vigorous reaction conditions (180 °C) and catalysis by tetrabutylphosphonium chloride result in disilylation of an internal alkene in low yield.[16] To improve reaction efficiency and control the stereochemistry of the reaction product, the reaction of internal alkenes may be rendered intramolecular by the use of a covalent tether between the alkene and the Si–Si-bonded functional group. This strategy was pioneered by Ito and offers a powerful means to elaborate simple organic compounds. The sequence in Scheme 4 is representative of the general concept.[17] Thus, homoallylic alcohol **12** was readily converted to **13** and then subjected to catalytic intramolecular disilylation with a Pd catalyst. It is considered that the disilylation occurs by cycle A wherein $Pd(OAc)_2$ is first reduced to Pd(0); consistent with this observation is that CpPd(allyl) is also effective, whereas other Pd(II) salts are not. The stereocontrol in the conversion of **13** to **14** can be rationalized according to the cyclic chelated structure **16** wherein the lowest energy chair conformer is one that participates in the reaction. Oxidation of the disilyl reaction products is readily accomplished in good yields, and the overall sequence provides a unique method for diastereoselective alkene dihydroxylation.



Scheme 4

Comprehensive studies by Ito have shown that a variety of silanyl substrates participate in the intramolecular disilylation reaction.[18] The chelated model **16** in Scheme 4 predicts the outcome of many substrates bearing different tethers, substitution patterns, and stereochemistry. As shown in Table 1, both *cis* and *trans* internal alkenes react efficiently and with good selectivity. The reaction of trisilane in entry 1 is selective for the construction of the five-membered siloxane over an alternative six-membered structure, an observation that is consistent with studies showing that bishomoallylic alcohol-derived substrates are less reactive than homoallylic alcohol derivatives. The stereochemical course of the reaction in entry 6 suggests that the allylic substituent is the dominant stereocontrol element in these reactions (Table 2).

Table 2 Catalytic intramolecular disilylation of alkenes

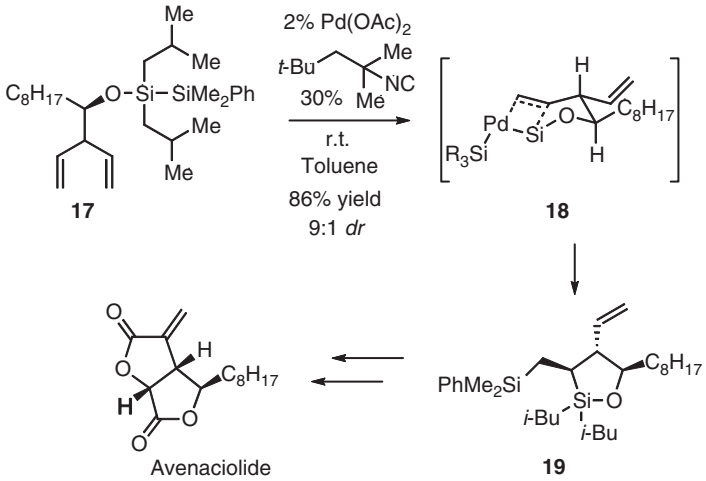
Entry	*Substrate*	*Product*	*% Yield*	dr	*Reference*
1			91	>95:5	17c
2			92	>99:1	17b
3			70	88:12	18
4			72	95:5	18
5			92	96:4	18
6			96	82:18	18

An excellent synthetic application of the intramolecular disilylation is depicted in Scheme 5.[19] The cyclic transition structure that operates in the disilylation reaction causes one of the two diastereotopic vinyl groups in **17** to preferentially participate in the reaction; transition structure **18**, wherein the maximum number of equatorial substituents are retained, appears to be preferred. Product siloxane **19** contains all of the stereochemical elements of the natural product and was converted to the target by a sequence involving hydroboration of the pendant olefin and oxidation of the C–B and C–Si linkages.

4.16.2.2 Diboration of Alkenes

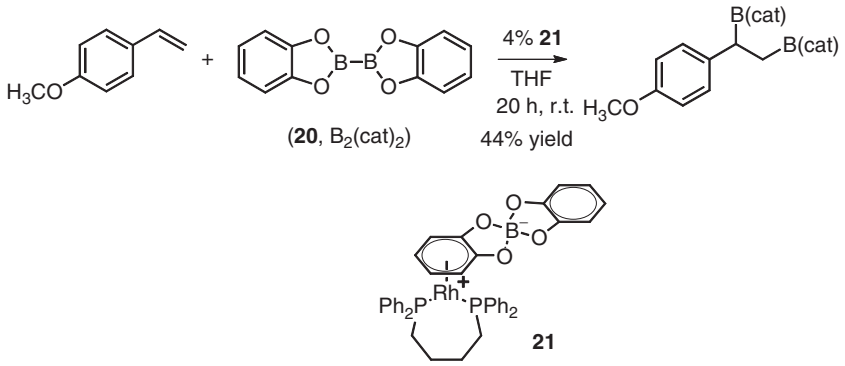
4.16.2.2.1 Rhodium-catalyzed diboration of alkenes

The catalytic diboration of alkenes was first reported in 1995 and employed bis(catecholato)diboron (**20**) in conjunction with either an Rh or a Au catalyst (equations 5 and 6).[20] Although catalysis with rhodium has become much more common, it is interesting to note that in the original report, gold catalysts were actually more effective. Catalysis with rhodium was based on an earlier report that described the oxidative addition of $B_2(cat)_2$ with Rh(I) to give bis(boryl)Rh complexes and a report that bis(boryl)rhodium complexes react with alkenes to give the product of alkene 1,2-diborylation.[21] In the catalytic version depicted in equation 5, the predominant side products arise from β-hydrogen elimination that generates vinyl boronates along with concomitant formation of hydroboration products. The gold catalyst avoids this problematic side reaction presumably because of the diminished stability of gold hydrides. Subsequent studies have shown that catalysis with Rh complex **21** occurs at room temperature and can apply to unstrained internal alkenes and that the transformation occurs by *syn* addition across the alkene.[22] Thus the reaction in equation 5 would appear to occur by cycle A. A more effective rhodium catalyst is related to **21**, but employs diphenylphosphinomethane (dppm) instead of 1,4-bis(diphenylphosphino)butane. This catalyst, (dppmRh (η^6-catBcat)), was crystallographically characterized and showed to affect room-temperature diboration of a number of alkenes including unstrained internal alkenes such as *trans*-β-methylstyrene. Side product formation, arising from β-hydride elimination, is significantly diminished with the dppm-derived catalyst. This observation is remarkable in that β-hydride elimination is

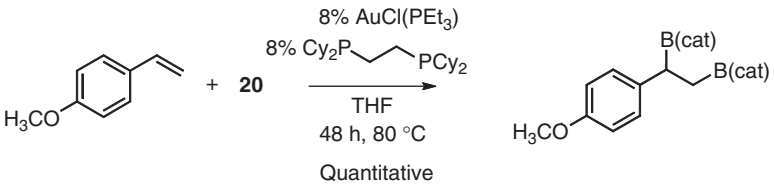


Scheme 5

likely competitive with reductive elimination in cycle A and small bite angle ligands generally inhibit the latter reaction. It must be concluded that for these systems, the β-hydride elimination from organorhodium intermediates is inhibited by ligands with small bite angles.

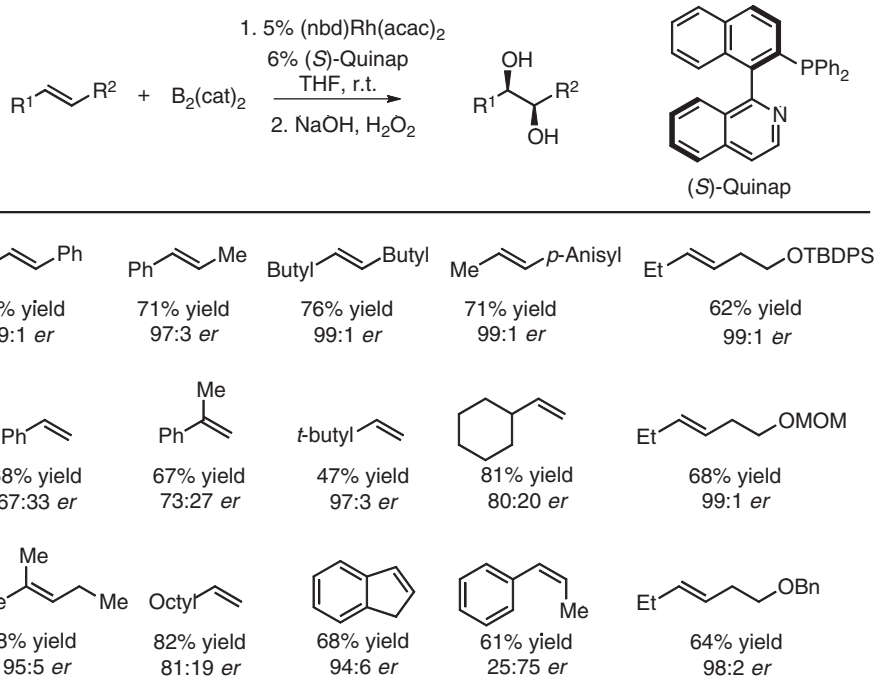


(5)

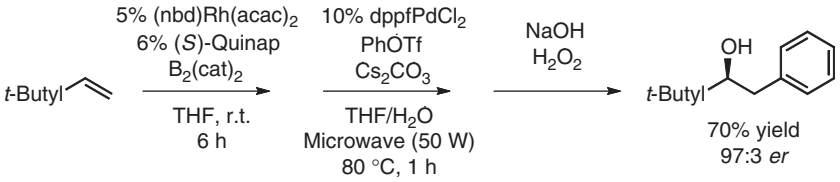


(6)

The synthetic utility of the rhodium-catalyzed diboration is considerably expanded by the development of an enantioselective variant (Scheme 6).[23] In the presence of rhodium and (*S*)-Quinap, diboration of a range of alkenes proceeds efficiently and, for *trans*-alkenes, the enantioselection is uniformly high. Selectivity is high for indene, but with other *cis*-alkenes, levels of enantiocontrol are diminished. When terminal alkenes bear an adjacent quaternary center, they can react with excellent levels of selectivity, but with simple linear α-olefins enantioselectivity hovers near 80:20 *er*. Lastly, trisubstituted olefins react with high levels of stereocontrol; however, reactions of these substrates are so sluggish that they lack synthesis utility. An important point of mention is that the catecholboronate esters are not stable to silica gel chromatography; however, they can be directly oxidized at the end of the reaction and furnish the derived 1,2-diols. An alternative transformation that applies to the 1,2-bis(boronate) intermediates involves tandem diboration Suzuki cross-coupling. As depicted in equation 7, subjection of the reaction mixture to an aryl halide and a Pd catalyst in the presence of Cs_2CO_3 in tetrahydrofuran (THF)/H_2O results in selective cross-coupling to the primary boronate, and the remaining secondary boronate can then be subjected to oxidative workup.[24] Of note, the entire sequence in equation 7 can be accomplished in a single reaction vessel.



Scheme 6

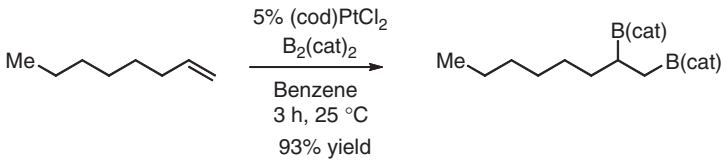


(7)

4.16.2.2.2 Platinum-catalyzed diboration of alkenes

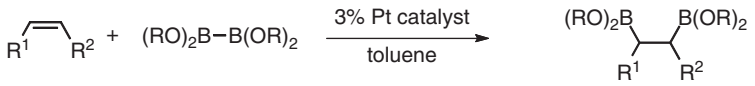
Shortly after the Rh-catalyzed diboration was introduced, Miyaura[25] and Smith[26] independently reported the Pt-catalyzed diboration of alkenes. Mechanistic studies on alkyne diboration[27] suggested that phosphine dissociation from $(R_3P)_2Pt(Bcat)_2$ is required for alkyne insertion (cycle A), and this stimulated the examination of phosphine-free Pt complexes. Suitable complexes are $Pt(cod)_2$, $Pt(nbe)_3$, and $Pt(dba)_2$, and it has been shown by the addition of mercury to the reaction mixture that these reactions are examples of homogeneous catalysis. As shown in **Table 3**, both $B_2(pin)_2$ and $B_2(cat)_2$ can be employed in this reaction although the reactions with $B_2(pin)_2$ generally require a higher temperature and longer reaction times (10–30 min at room temperature vs. 1 h at 50 °C). For the $Pt(dba)_2/B_2(pin)_2$ reactions (entries 1–4), the addition of phosphine and arsine donors does not alter reactivity, suggesting that the phosphine/arsine-free catalysts are responsible for catalysis. Neither of the systems allows the clean diboration of unstrained internal alkenes.

The complex $(cod)PtCl_2$ is commercially available and has been used for the catalysis of diboration reactions (equation 8).[28] Reduction of Pt(II) to Pt(0) is an expected prerequisite for the reaction, and observations of the reaction are consistent with this transformation: The reaction exhibits an induction period (1 h), and when $(cod)PtCl_2$ is mixed with $B_2(cat)_2$, the reaction mixture darkens over the course of 5 h, during which time (cat)BCl is detected by ^{11}B nuclear magnetic resonance (NMR) (28 ppm). When this same reduction is conducted with $(cod)PtBr_2$, the reaction takes 24 h. Although the reduction does not occur at all with $(cod)PtI_2$, it is immediate with Cp_2Pt. These features suggest that $B_2(cat)_2$ reduces the Pt dihalide to Pt(0), presumably by a metathetical reaction that generates (cat)BCl and a Pt boryl, and that the reactivity follows the trend Cl > Br > I. In addition to diboration of α-olefins, this study also provided the first example of catalytic imine diboration (equation 9).



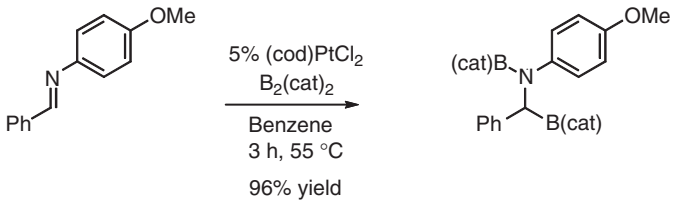
(8)

Table 3 Pt-catalyzed diboration of unactivated alkenes[a]



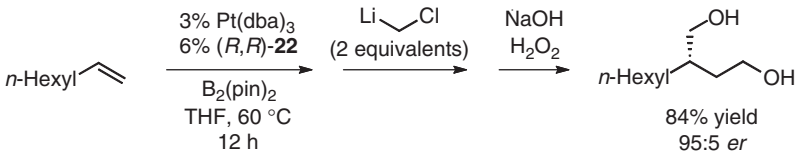
Entry	*Substrate*	*Catalyst*	*Diboron*	*% Yield*
1	1-Decene	3% $Pt(dba)_2$	$B_2(pin)_2$	82
2	Styrene	3% $Pt(dba)_2$	$B_2(pin)_2$	86
3	Cyclopentene[b]	3% $Pt(dba)_2$	$B_2(pin)_2$	85
4	*trans*-1,3-Pentadiene	3% $Pt(dba)_2$	$B_2(pin)_2$	94
5	Ethylene	3% $Pt(cod)_2$	$B_2(cat)_2$	84
6	1-Hexene	3% $Pt(cod)_2$	$B_2(cat)_2$	95
7	*p*-Methoxystyrene	3% $Pt(cod)_2$	$B_2(cat)_2$	90
8	6-Chloro-1-hexene	3% $Pt(cod)_2$	$B_2(cat)_2$	85
9	6-Acetoxy-1-hexene	3% $Pt(cod)_2$	$B_2(cat)_2$	88
10	Norbornene[c]	3% $Pt(cod)_2$	$B_2(cat)_2$	93

[a]Entries 1–4 from Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689 and entries 5–10 from Iverson, C. N.; Smith, M. R., III. *Organometallics* **1997**, *16*, 2757.
[b]Product is the *syn* stereoisomer.
[c]$Pt(nbe)_3$ used for this experiment, product is the *exo cis* addition product.

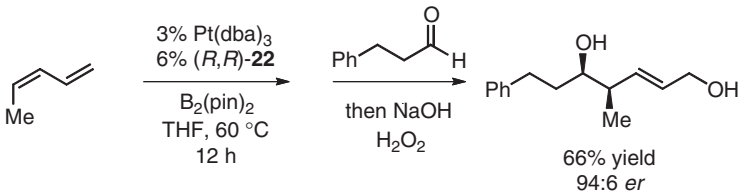


(9)

The studies described above suggest that phosphine-free complexes are the catalytically relevant species in platinum-catalyzed diboration. This would appear to preclude enantioselective catalysis with chiral phosphorus-based ligands. However, chiral phosphonites have been demonstrated to be extremely effective for controlling the stereochemistry in the diboration of α-olefins (Scheme 7).[29] These reactions can employ either $Pt_2(dba)_3$ or $Pt(dba)_3$, readily available from K_2PtCl_4, as the platinum source. With a catalyst loading of 3 mol% Pt and 6 mol% ligand **22**, diborations are generally complete in 12 h at 60 °C and furnish excellent levels of enantioselection. Of the ligands examined, taddol-derived phosphonites were more effective than phosphoramidites, although not by a significant degree. With respect to the substrate scope, α-olefins are generally excellent substrates for the reaction, and it is notable that both allylic alcohol derivatives and styrenes participate in the reaction. Terminal dienes bearing a *cis* substituent also undergo the 1,2-diboration with high levels of enantioselectivity employing ligand **22**.[30] Selectivity is enhanced for the 1,1-disubstituted dienes when ligand **24** is employed. Although all of the examples in Scheme 7 were oxidized to the derived 1,2-diol, it is notable that the intermediate diborons may participate in other reactions. In this respect, an important feature of these diboration reactions is that they only require the use of 1.05 equivalents of $B_2(pin)_2$, and they operate in an anhydrous solvent, thereby allowing subsequent reactions to be carried out without isolation of the intermediate diboron. Thus, tandem diboration/homologation[31]/oxidation directly furnishes enantiomerically enriched 1,4-diols from terminal alkenes (equation 10). Moreover, the 1,2-diboration of dienes provides reactive allylboronates that participate in addition to aldehydes and furnish enantiomerically enriched 1,5-diols on oxidation (equation 11).



(10)



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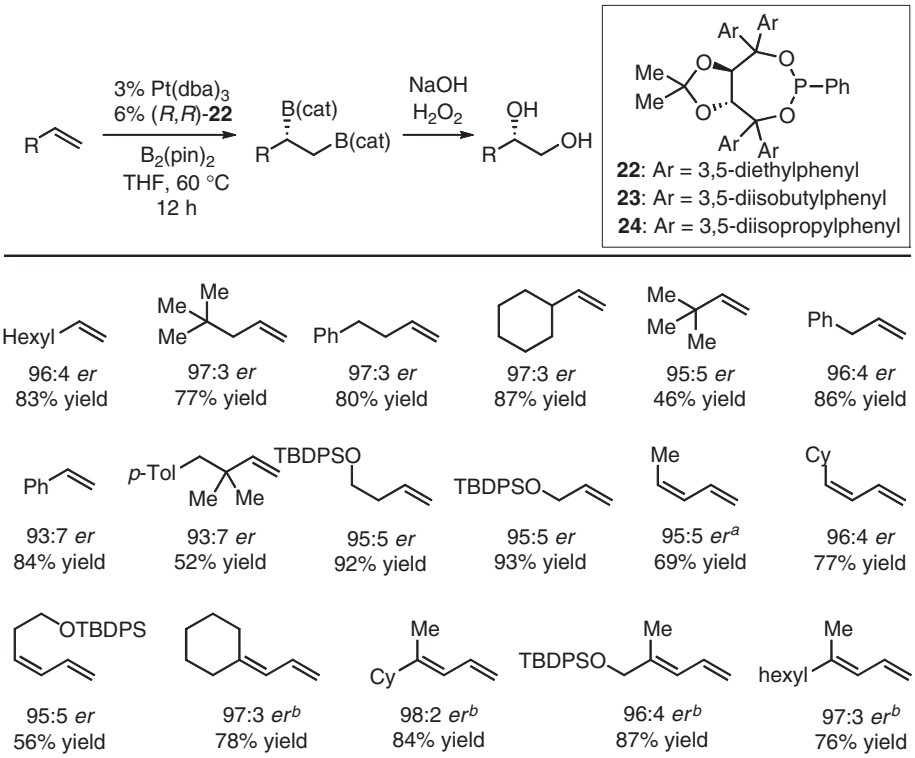
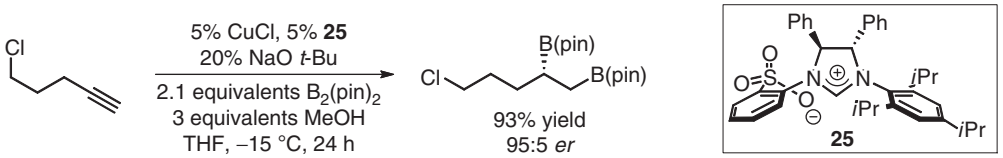


[a]With ligand **23.**
[b]With ligand **24.**

Scheme 7

4.16.2.2.3 Other metal-catalyzed diboration of alkenes

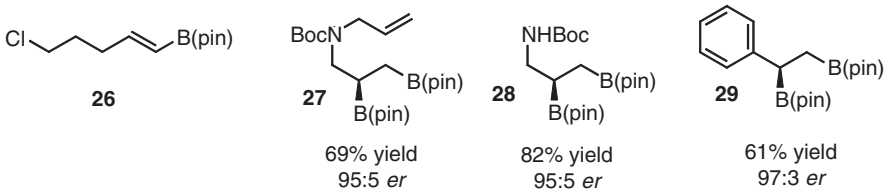
In addition to the Rh and Au-catalyzed alkene diborations described in Section 4.16.2.2.1, the diboration of alkenes with $B_2(cat)_2$ has been catalyzed by Au, Ag, and Cu nanoparticles as well as Au, Pt, Cu, Ag, Pd, and Au carbene complexes.[32] Although these advances may lay the groundwork for new research directions, an alternative to the Pt-catalyzed enantioselective alkene diboration is the copper-catalyzed enantioselective double hydroboration of alkynes.[33] This reaction is found on the observation that Cu(I) salts will undergo transmetallation with $B_2(pin)_2$ and generate copper–boryl complexes, species known to react with alkynes by a borylcupration process.[34] In the process depicted in equation 12 (Scheme 8), an intermediate terminal vinylboronate (**26**) is generated and participates in a subsequent hydroboration. A critical feature of carbene ligand **25** is that it allows regioselective hydroboration of the terminal alkyne, whereas monodentate carbenes provide regioisomeric mixtures leading to diminished enantioselectivity of the overall process. The products **27–29** illustrate other compound types that may be accessed with this technology. Impressively, product **27** demonstrates the complementary aspect of Cu-catalyzed alkyne double hydroborylation and Pt-catalyzed alkene diboration.



(12)

4.16.2.2.4 Metal-free catalytic diboration of alkenes

A remarkable observation is that the diboration of unactivated olefins can be catalyzed by inorganic alkoxide bases in the presence of methanol (Table 4).[35] Although nucleophilic additives have been shown to facilitate addition of $B_2(pin)_2$ to activated alkenes in a conjugate borylation fashion, it is entirely unexpected that 1,2-addition should proceed with nonpolar substrates. To effect this transformation, 15 mol% of a metal alkoxide and 5 equivalents of methanol are employed in THF solvent. Although Cs_2CO_3 is most commonly employed, Na, K, and Li methoxides and *tert*-butoxides are equally effective. It is also noteworthy that $B_2(cat)_2$



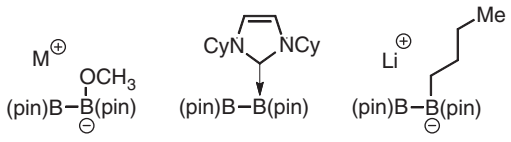
Scheme 8

Table 4 Metal-free diboration of alkenes

Entry	*Substrate*	*Base*	*Product*	*% Yield*[a]
1	Hexyl	Cs_2CO_3	Hexyl, B(pin), B(pin)	71
2		Cs_2CO_3	B(pin), B(pin)	71
3	Ph	NaO*t*-Bu	Ph, B(pin), B(pin)	74
4	Me, Me	Cs_2CO_3	Me, Me, B(pin), B(pin)	57[b]
5	Me, Me	Cs_2CO_3	Me, B(pin), B(pin), Me	69[c]
6		NaO*t*-Bu	B(pin), B(pin)	65

[a]Isolated yield of diboron compound.
[b]Diastereoselection is 97:3, determined on oxidation to the derived 1,2-diol.
[c]Diastereoselection is 95:5, determined on oxidation to the derived 1,2-diol.

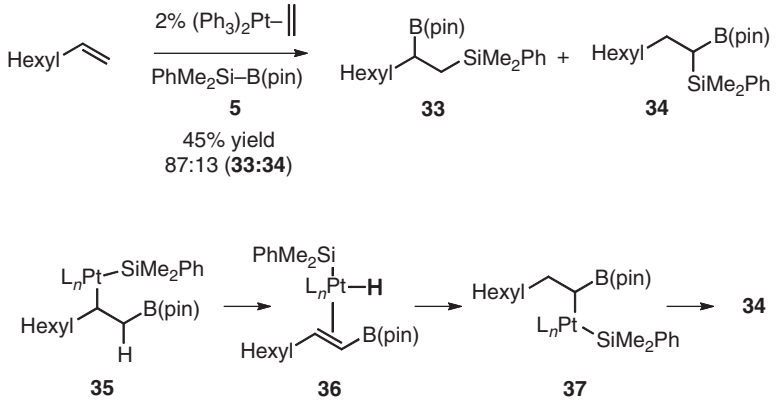
and B_2(neopentylglycolato)$_2$ can be employed with similar outcomes. The process generally gives good yields with minimal amounts of hydroboration products even though protic methanol is employed in the reaction. A critical intermediate in these reactions is suggested to be the methoxide · $B_2(pin)_2$ adduct (**30**), a species that has been detected[36] in reactions between Verkade's base, methanol, and $B_2(pin)_2$, and that is related to a Lewis acid–Lewis base adduct formed between KO*t*Bu and $B_2(pin)_2$.[37] The enhanced reactivity of these reagents finds precedent in NHC · $B_2(pin)_2$ (**31**)[38] and BuLi · $B_2(pin)_2$ (**32**)[39] adducts that have been shown to exhibit enhanced nucleophilicity of the boron reagent and enable conjugate additions and allylic substitutions.



4.16.2.3 Other Alkene Bismetallations

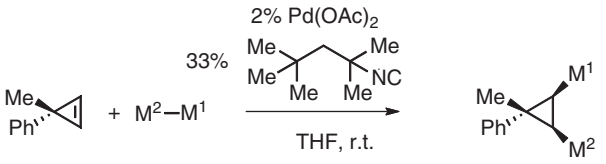
Silylboration of alkene substrates has the benefit that the silicon and boron atoms can be sequentially replaced with different functional groups in the course of a reaction sequence. These reactions were first introduced by Suginome and Ito, and employed silylboron reagent **5** in the presence of a Pt(0) catalyst.[40] 1-Octene reacts with **5** in the presence of 2% of $(PPh_3)_2$Pt(ethylene) or

$Pt(PPh_3)_4$ to give the derived silylboration product (Scheme 9). $Pd(PPh_3)_4$ and $Pd(OAc)_2$/*tert*-alkylisocyanide catalysts are ineffective in this reaction and, surprisingly, the more basic complex $(PhMe_2P)_2Pt$(ethylene) exhibited diminished reactivity. The predominate addition mode delivers the 2-boryl-1-silyl regioisomer **33**, with a minor adduct being the 1,1-silylboration product **34**. In addition to 1-akenes, styrenes and ethylene are also reactive. A mechanism corresponding to cycle A is proposed, and it can account for the generation of the 1,1-silylboration product: subsequent to oxidative addition, a minor reaction path may be an insertion reaction to deliver the internal C–Pt-bonded compound **35**. Isomerization of **35**–**37**, a precursor to 1,1-addition product **34**, may occur by a mechanism involving β-hydrogen elimination/hydrometallation through the intermediacy of olefin complex **36**.



Scheme 9

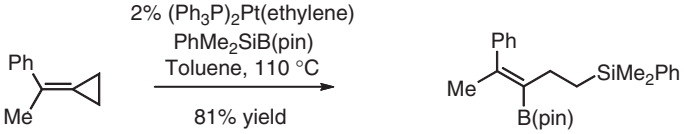
Silylstannation and distannylation of strained cyclopropenes are effective methods to construct substituted cyclopropane moieties in a stereoselective fashion.[41] Similar to disilylation, these reactions are catalyzed by $Pd(OAc)_2$ in the presence of a tertiary isocyanide ligand. As shown in equation 13, the stereochemistry in these reactions appears to be dominated by steric effects.



(13)

M^1, M^2 = $SnMe_3$: 83% yield
M^1 = $SiMe_3$, M^2 = $SnBu_3$: 94% yield

Suginome and Ito studied the Pd-catalyzed silylboration of methylenecyclopropanes (MCPs).[42] As shown in equation 14, silylboration of these substrates results in the rupture of the three-membered ring and creation of β-silylvinylboronates. The regioselectivity and stereoselectivity of the reaction depend on both the metal (Pd or Pt) and the ligand structure. Mechanistically, these reactions may proceed by borylpalladation of the MCP alkene, followed by ring opening; an alternate pathway involves oxidative addition of the catalyst to a C–C bond of the cyclopropane substrate. In the case of *meso*-substrates (e.g., equation 15), the ring opening creates a chiral compound, and this can be controlled effectively with chiral monophosphine ligand **38**. The synthesis utility of this transformation is evident in the sequence depicted in equation 16. Subsequent to the silylborative ring opening, boronate homologation provides an allylboron, which engages an aldehyde in a selective fashion. The stereocontrol in equation 16 may arise from the transition structure **39**, wherein the allylic H atom is directed toward the large pinacolatoboronate and the newly introduced silicon group is directed away from the transition state array.



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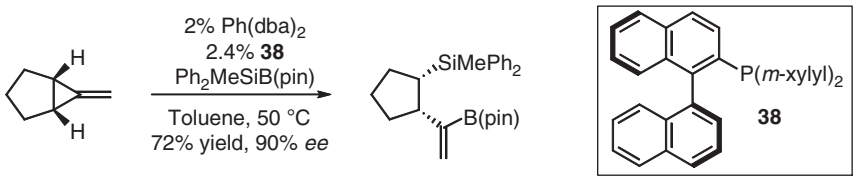

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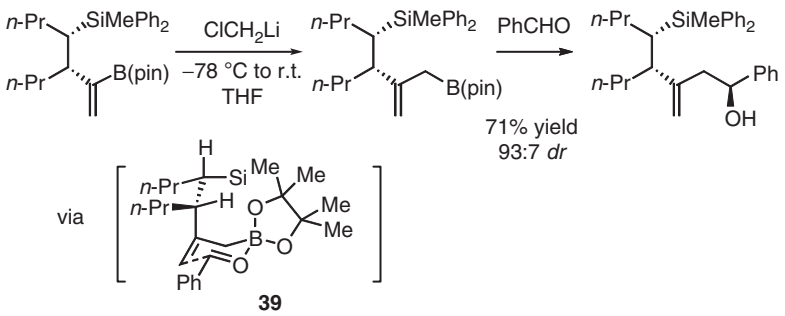
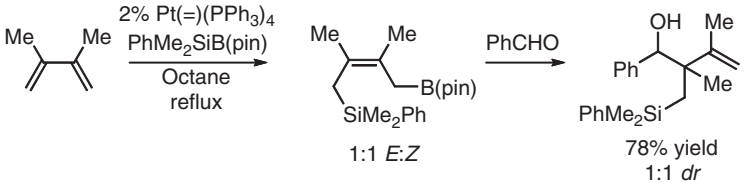


(16)

4.16.2.4 Bismetallation of Dienes

The disilylation of dienes has been known since the 1970s, with first reports originating from the Kumada laboratories.[43] These studies have shown that 1,4-addition across the diene was the predominant pathway, with diene dimerization being a commonly observed side product. Both Ni(0) and Pd(0) complexes were efficacious for the reaction, and a variety of electron-neutral and electron-deficient halogenated disilanes have proven to be reactive. Although these processes have laid the foundation for the development of silylboration and diboration reactions, from a synthesis standpoint the disilylations have yet to gain significant traction.

In 1998, Ito reported the Pt-catalyzed silylboration of dienes and studied the related allylation reactions.[44] An interesting feature of these reactions is that the diastereoselection in the silylboration itself is low (approximately 1:1 *E*/*Z* ratio; equation 17), whereas the stereoselection of the three-component reaction is excellent (>99:1 *dr*; equation 18). This finding suggests that rather than a two-step process wherein the 1,4-silylboration product is first generated and then consumed in an allylation, the reaction more likely occurs by interception of an intermediate allylplatinum complex (i.e., **40**). In addition to the stereochemical outcome of the reaction, the connectivity of the reaction products is also reflective of a diverted allylplatinum intermediate. With cyclohexadiene, the 1,4-silylboration generates a chiral product and the configuration may be controlled by the use of chiral ligands. This feature was studied by Moberg, and it was found that with Pt(0) in the presence of the phosphoramidite (binol)P(N*i*Pr$_2$)$_2$, enantioselectivities close to 70% *ee* could be obtained.[45]



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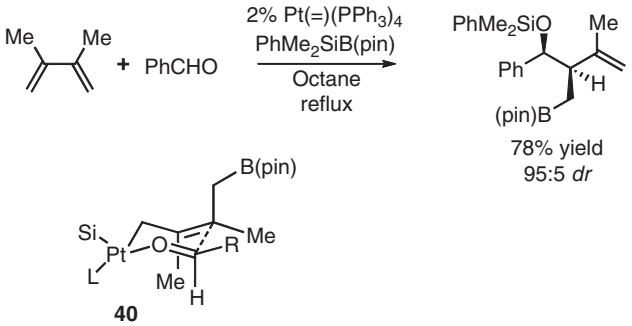
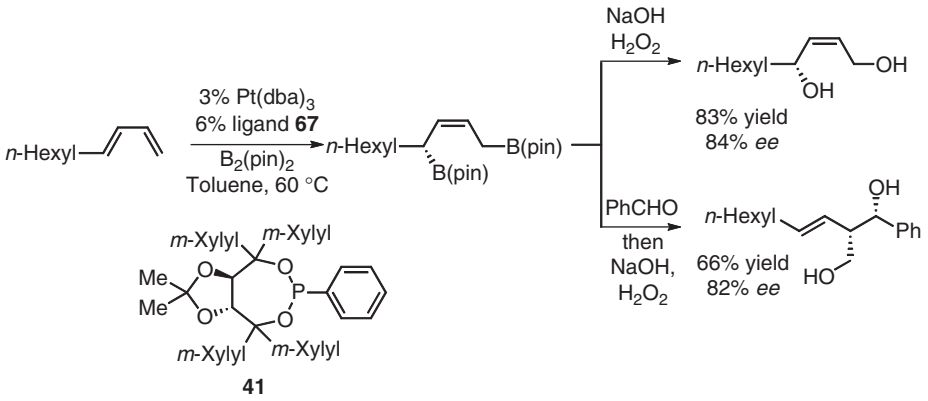


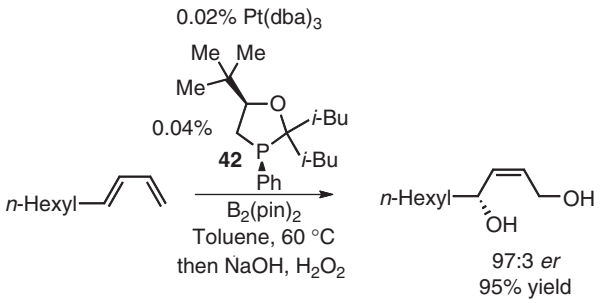
(18)

The diboration of dienes was first investigated by Miyaura and it was found that Pt(0) complexes were highly effective in this transformation.[46] Interestingly, the nature of the ligand has a significant control over the 1,2:1,4 selectivity. With phosphine-based platinum complex $Pt(PPh_3)_4$ 1,4-addition is the predominant outcome, whereas with phosphine-free platinum complex $Pt(dba)_2$, 1,2 selectivity is observed. With chiral taddol-derived phosphonite ligand (i.e., **41**), the reaction exhibits good levels of enantiocontrol furnishing 1,4-bis(boronates) that can be oxidized to synthetically useful 1,4-diols or that can engage in subsequent carbonyl allylation reactions (Scheme 10).[47]



Scheme 10

Significantly improved levels of enantioselection and outstanding levels of catalyst productivity are obtained when oxaphospholane ligand **42** is employed in the 1,4-diene diboration reaction (equation 19).[48] Oxaphospholane ligands are electronically similar to aryldialkyl phosphines, and it has been observed in a number of studies that electron-rich ligands can accelerate diborations (*vide supra*). Remarkably, the level of ligand acceleration is high enough that enantioselection is still excellent even when the ligand:metal ratio is 0.5:1.

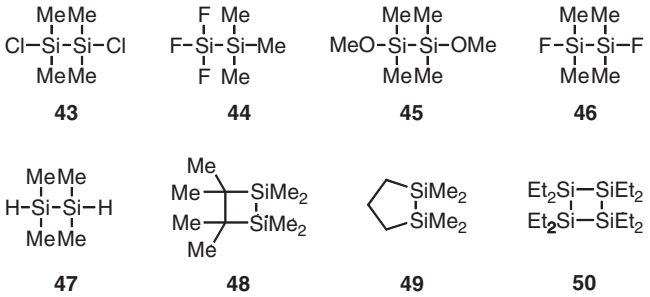


(19)

4.16.3 Bismetallation of Alkynes

4.16.3.1 Disilylation of Alkynes

Disilylation of alkynes was among the first class of catalytic bismetallations studied and their development introduced many of the catalytic systems that are used in other areas of bismetallation chemistry.[49] Investigations revealed that electron-deficient disilanes (i.e., **43–46**), nonhindered hydrodisilanes (i.e., **47–48**), and strained cyclic disilanes (i.e., **49–50**) exhibit enhanced reactivity relative to hexaalkyldisilanes (i.e., $Me_3SiSiMe_3$), which is often unreactive. Early studies established many of the prominent reactivity features. For example, the reaction in equation 20 represents one of the first catalytic alkyne disilylation reactions and documents *cis* addition of the disilane across the alkyne. In this study, it was found that at least one hydrogen on the disilane reagent is imperative for catalysis; $Me_3SiSiMe_2H$ is reactive, whereas $Me_3SiSiMe_3$ is not.



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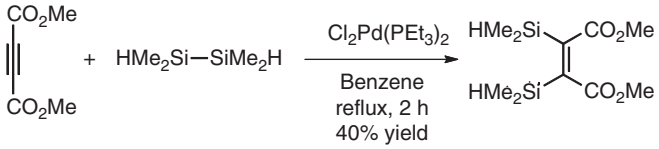
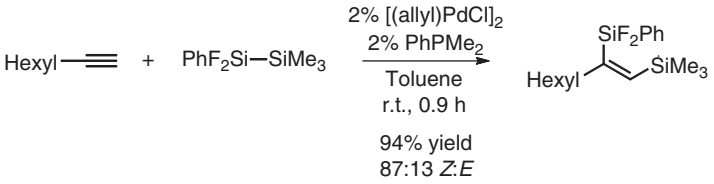


When disilane reagents are nonsymmetric, a trend emerges that the more electron-deficient silicon atom is added to the internal position of nonsymmetric alkynes (equations 21–22).[50] It has been suggested that the bis(silyl) palladium intermediate that would operate in equation 21 via cycle A experiences a stronger bonding between Pd and the fluorinated silane; thus, alkene insertion into the nonfluorinated silane might be expected to occur first. If this is the case, then it can be inferred that the insertion reaction occurs in a manner that positions the Pd atom on the internal carbon of the substrate, a regioselectivity mode that has been observed in other bismetallations.[51] The reaction in equation 21 also demonstrates the feature that the reaction of alkynes are much faster than those of alkenes; the catalyst system in equation 21 requires 100 °C for the disilylation of 1-octene.



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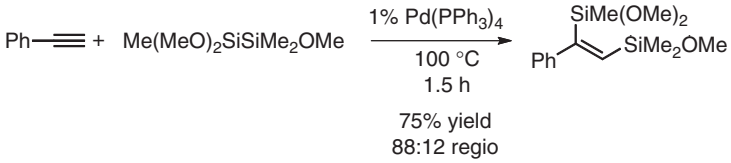
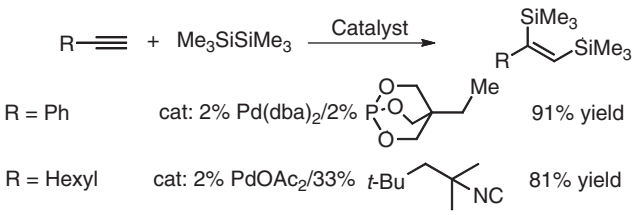


(22)

It has been well documented that Pd and Pt undergo oxidative addition to Si–Si linkages and that the resulting bis(silyl) metal complex can transfer both the silicon atoms to an unsaturated substrate.[52] In a comprehensive study, Fink showed that the oxidative addition is facilitated by Lewis basic small bite angle bidentate diphosphines that bear large phosphorous substituents.[53] For example, the electronic properties and the bite angle of dicyclohexylphosphinoethane (dcpe) facilitate oxidative addition with $HMe_2SiSiMe_2H$ giving the four-coordinate square planar $(HMe_2Si)_2Pd(dcpe)$ (**51**) complex, which was characterized by X-ray crystallography. The cyclohexyl substituents are thought to offer kinetic stabilization to the complex. In stoichiometric reactions, **51** transfers both silicon atoms to dimethylacetylene dicarboxylate in a *cis* fashion and is competent for the catalytic reaction as well. It should be noted that this result contrasts with observations by Ozawa and Hayashi that disilylation is inhibited by 1,3-bis(diphenylphosphino)propane, 1,2-bis(diphenylphosphino)ethane (dppe), and bis(diphenylphosphino)ferrocene (dppf), presumably because the four-coordinate complex that arises on oxidative addition with the disilane is resistant to phosphine dissociation and olefin insertion.[14]

Two-catalyst systems provide exceptional activity and allow catalytic disilylation with unreactive hexaalkyldisilanes. As depicted in equation 23, in the presence of a constrained bicyclic trialkylphosphite, Pd-catalyzed disilylation with $Me_3SiSiMe_3$ can be accomplished in an efficient fashion for phenylacetylene.[54] Similar levels of reactivity are offered with the *tert*-alkyl isocyanide ligand. Notably, in the presence of Pd/*tert*-alkylisocyanide intramolecular disilylation can be accomplished in good yields and with excellent stereoselection with an internal alkene substrate (equation 24).[55] For mechanistic reasons, the reaction in equation 25 merits mention.[56] In this example, the net result is the product of disilylation although a Si–Si-bonded

reagent is not involved. Instead, a plausible rationale is that subsequent to oxidative addition with the SiH bond, σ-bond metathesis generates H_2 and bis(silyl)platinum intermediate **52**. This compound can then participate in disilylation of the alkyne. The fact that a hydrido;(silyl)platinum intermediate is involved can be inferred from the detection of 1,1-disilylation product **53** in some reactions.



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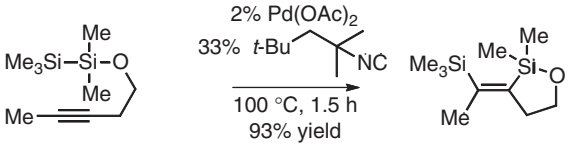

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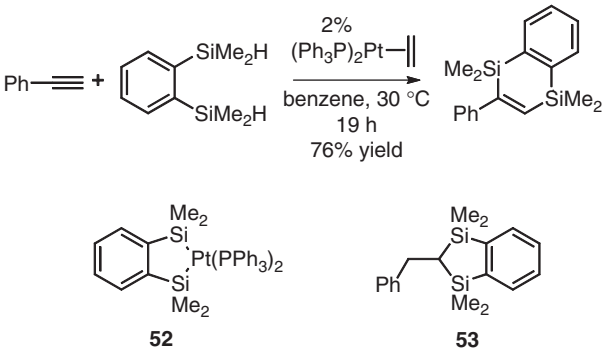
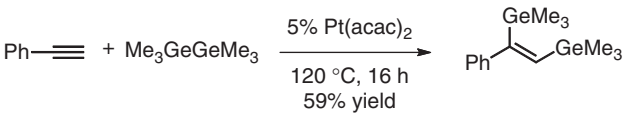


(25)

4.16.3.2 Digermylation of Alkynes

The digermylation of alkynes has been described and is analogous to the disilylation of alkynes. The catalytic reaction has many of the same features and can employ electron-deficient reagents, strained cyclic reagents, and, with forcing conditions, hexaalkyldisilanes (equation 26).[57]

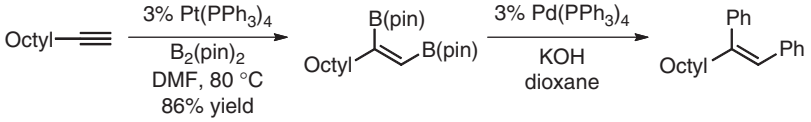


(26)

4.16.3.3 Diboration of Alkynes

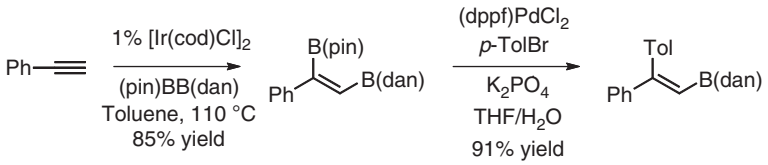
Diboration of alkynes can be accomplished with a number of catalyst systems and, coupled with the methods for transformation of organoborons, provides a powerful method to construct olefinic compounds. With platinum catalysis, diboration often occurs efficiently for both terminal and internal alkynes and in a *cis*-selective fashion (equation 27). In the original report by Miyaura, NMR evidence was collected that established oxidative addition of the $B_2(pin)_2$ to $Pt(PPh_3)_4$, and it was therefore proposed that these reactions occur by a cycle A mechanism.[58] Subsequent studies resulted in crystallographic characterization of bis(boryl)platinum complexes. Smith and Marder studied the detailed mechanism of these reactions and demonstrated that a sequence involving oxidative addition, phosphine dissociation, and alkyne coordination/insertion operates.[59] This feature provides an understanding for the observations that dppe-derived complexes are inactive, excess phosphine inhibits the reaction, and $(PPh_3)_2P(o\text{-tolyl})$-derived catalysts exhibit superior activity compared with their PPh_3-derived counterparts.

This mechanism may also provide a vehicle for understanding as to why some terminal alkynes are less reactive than internal alkynes; with decreased steric hindrance, the π-acidic terminal alkyne may coordinate to $L_2Pt(0)$ and inhibit the oxidative addition.



(27)

From a synthetic standpoint, several studies are important. It has been shown that the readily available air-stable complex $(cod)PtCl_2$ is effective in alkyne diboration using B_2cat_2.[28] Nonsymmetric diboron reagent **54** also undergoes regioselective diboration in the presence of both Pt(0) and Ir(I) complexes (equation 28). In this reaction, the dansyl-protected boron atom is delivered to the terminal carbon, and it is likely that the electron donation from the nitrogen atoms renders the B less prone to transmetallation; the more hindered pinacol group can be selectively reacted in cross-couplings.



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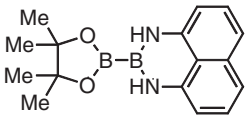
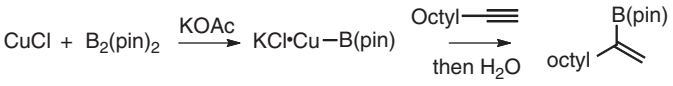


(pin)BB(dan), **54**

Miyaura demonstrated the ability of CuCl to undergo KOAc-promoted transmetallation with $B_2(pin)_2$ delivering a CuB(pin) complex that adds to alkynes, enones, and allylic chlorides in a stoichiometric fashion (equation 29).[34] Yoshida subsequently showed that both the boryl groups could be added to alkynes directly if higher temperatures were employed and proton sources were absent from the reaction mixture.[60] Moreover, this reaction applies to transiently generated alkynes such as benzyne (equation 30).



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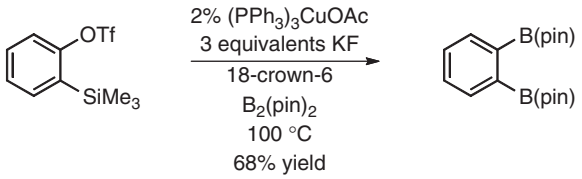
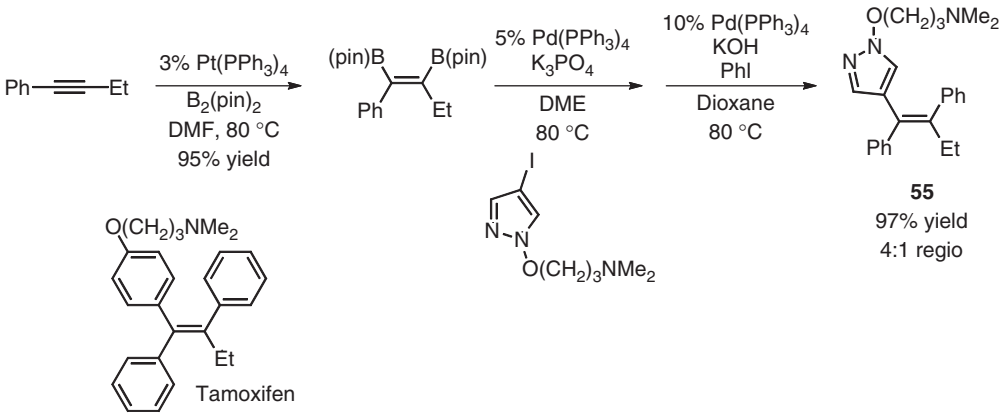


(30)

The alkyne diboration is well disposed for the construction of stereochemically defined tetrasubstituted olefins. Along these lines, derivatives of the anticancer agent tamoxifen have been targeted with these strategies. As depicted in **Scheme 11**, analogs such as **55** can be prepared by a sequence involving alkyne diboration followed by two sequential Suzuki couplings.[61] The first cross-coupling is proposed to be favored adjacent to the arene because the electron-withdrawing nature of the aryl ring promotes transmetallation.

4.16.3.4 Silylboration of Alkynes

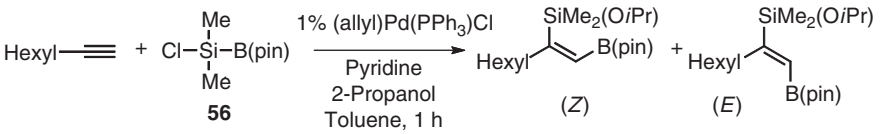
The silylboration of alkynes offers one of the most versatile strategies for the construction of functionalized olefins. With appropriate catalysts, one can control the regioisomer and the stereoisomer of silylboration product. Catalytic cross-coupling can be directed to occur at either the organoboronate site or the organosilane site such that selective introduction of different organic electrophiles can be accomplished. Mechanistic studies with platinum complexes have shown that this elementary step is



Scheme 11

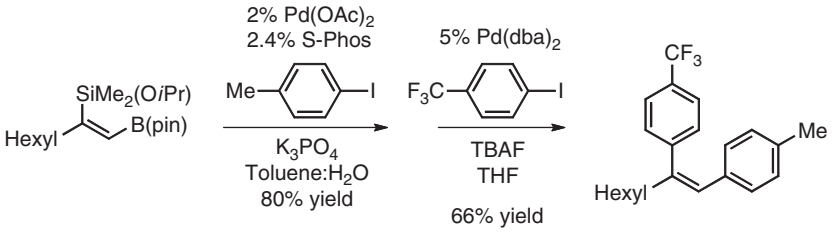
facilitated with Lewis acidic boron reagents and Lewis basic phosphine ligands and, like many cycle A processes, it appears that phosphine dissociation is required. Isolation and characterization of alkyne insertion products have shown that insertion of the alkyne into the C–B bond, as opposed to the C–Si bond, is the preferred pathway. This preference likely arises because the involvement of the empty p orbital on boron allows the insertion reaction to occur with less reorientation of the boron atom (relative to Si). It is also of note that the insertion appears to favor the internal C–Pd bond when terminal alkynes are the substrate.

In one very useful manifestation of the silylboration reaction, either stereoisomers of the silylboration adduct can be generated by simply manipulating the stoichiometry of the reaction.[62] Thus, with excess alkyne the reaction in equation 31 shows excellent *Z* selectivity. However, when excess silylboron is employed, the *E*-isomer predominates. The selectivity appears to arise through a changeover from kinetic control (excess alkyne) to thermodynamic control (excess silylboron). Sequential cross-couplings can be achieved with both the *Z* adduct (equation 32) and the *E* adduct (not shown), and provide an excellent means to generate stereodefined trisubstituted alkenes.



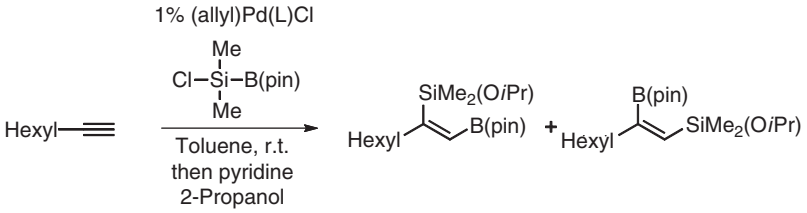
(31)

Excess alkyne (1.2 equivalents): >99:1 *Z*:*E* (91% yield)
Excess **56** (1.2 equivalents): 11:89 *Z*:*E* (85% yield)



(32)

While the silylboration of terminal alkynes with $PhMe_2SiB(pin)$ and $PhMe_2SiB(cat)$ has been shown[63] to reliably furnish 1-boryl-2-silylalkenes, with $ClMe_2SiB(pin)$ the regiocontrol can be manipulated with the choice of the ligand (equation 33).[64] Mechanistic experiments are highly suggestive of a scenario where cycle A operates for both the conditions. In the reaction with PPh_3 as the ligand, olefin migratory insertion into a Pd–B bond is irreversible and dictates the regiochemistry of the reaction, whereas with the more basic ligand $(t\text{Bu})_2$P(2-biphenyl), reductive elimination is slow and renders the insertion reversible by a β-boryl elimination pathway; reductive elimination is thus the regioselectivity determining event and is favored at the least hindered carbon atom.

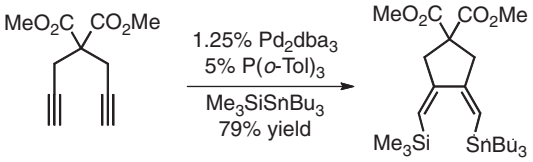


(33)

L = PPh_3: >99:1 (85% yield)
L = (*t*-Bu)$_2$P(2-biphenyl): 3:97 *E*:*Z* (90% yield)

4.16.3.5 Other Bismetallations of Alkynes

In the course of studying the stannylboration and silylboration of alkynes, Tanaka[65] discovered a bismetallative cyclization of diynes and enynes. These reactions were extended to the silylstannation of diynes by Rajanbabu.[66] As the experiment in equation 34 shows, this transformation proceeds in good yield and excellent levels of stereocontrol to deliver a compound with possible helical chirality. NMR experiments showed restricted bond rotation in the product at −40 °C, but not at room temperature. Mori extended the bismetallative cyclization to the silylstannation of enynes and examined a range of substrates that deliver heterocyclic ring systems.[67] The remarkable example in equation 35 shows that this transformation can be used to create compounds with a new ring and four new stereochemical elements, all with exquisite levels of stereocontrol.



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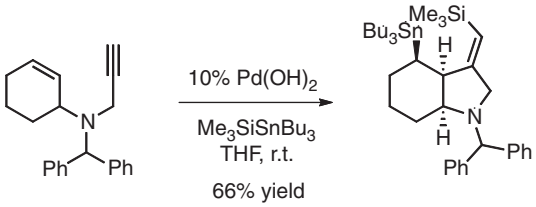


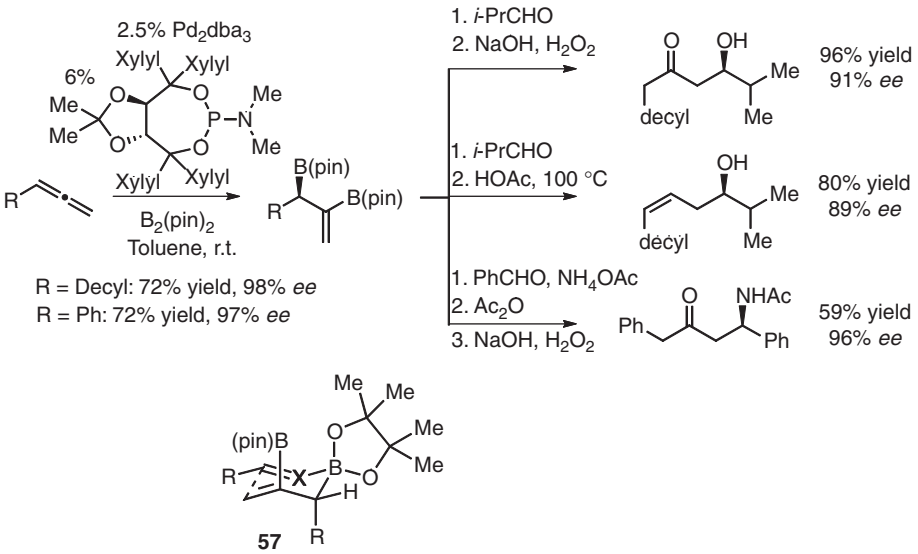
(35)

4.16.4 Bismetallation of Allenes

4.16.4.1 Diboration of Allenes

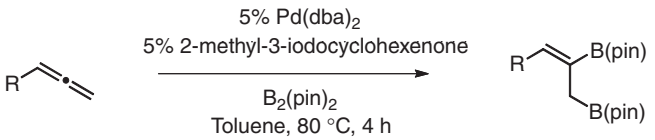
The catalytic diboration of allenes was first described in 1998 and this process holds promise for asymmetric synthesis.[68] With terminal allene substrates, regioselectivity is a critical issue and the product outcome hinges on the reaction conditions. With Pt(0) or Pd(0) catalysts, in the presence of Lewis basic phosphine ligands, diboration of the internal alkene is the primary reaction product. Notably, this reaction has been rendered enantioselective with chiral phosphoramidite ligands and the subsequent diboron products can be engaged in a number of subsequent organic transformations.[69] As depicted in **Scheme 12**, the allene diboration products will undergo allylboration of aldehydes or imines via transition structure **57** and deliver *β*-hydroxy[70] and *β*-amino[71] vinyl boronates with excellent levels of chirality transfer. The intermediate vinyl boronate may then be oxidized or protonated as depicted in **Scheme 12** or used in cross-coupling or halogenation (not shown) reactions. Mechanistically, the allene diboration has been shown to proceed by cycle A, and the isotope-labeling studies indicate that the process proceeds by initial insertion of the terminal alkene into the Pd–B bond furnishing a *π*-allyl palladium complex.[72]

When a catalytic amount of an organic iodide is added to the allene diboration reaction, the transformation takes a different course and the boron atoms are added across the terminal alkene of the substrate.[73] This reaction has been shown to proceed by cycle B, wherein (pin)BI, generated by reaction of the organic iodide, participates in the oxidative addition. The 1,2-bis(boronates) from this reaction are generated in high *Z*:*E* selectivity (**Table 5**) and in excellent yields, and the reaction products appear well disposed for use in stereoselective synthesis.



Scheme 12

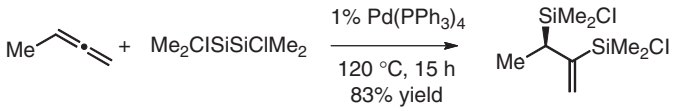
Table 5 Pd-catalyzed diboration of allenes



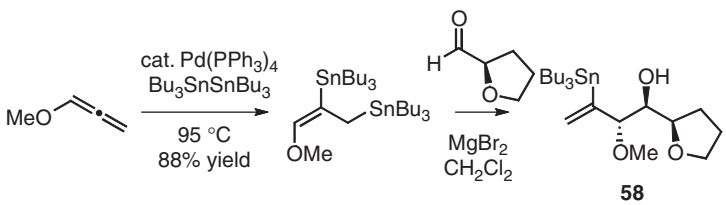
Entry	*R*	*% Yield*	Z:E
1	Butyl	88	94:6
2	Ph	87	95:5
3	Cyclohexyl	85	94:6
4	Cyclopentyl	86	95:5
5	PhO	86	94:6

4.16.4.2 Disilylation, Distannylation, and Silylstannation of Allenes

The catalytic addition of disilanes, distannanes, and silylstannanes to allenes is readily catalyzed by group 10 metals, most commonly Pd(0) and Pt(0) complexes. Watanabe found that the disilylation in equation 32 could be accomplished in excellent yield with $Pd(PPh_3)_4$ furnishing the internal addition product.[74] $Pd(PPh_3)_4$ is also an effective catalyst for the silylstannation and distannylation of allenes, with the internal addition product being the kinetic product; however, prolonged heating of the reaction mixture results in conversion to the thermodynamic terminal addition product.[75] The utility of the allene distannylation products is evident from studies by Williams, who demonstrated that these compounds participate in chelation-controlled allylmetallation reactions furnishing stannylated homoallylic alcohols such as **58**.[76] The intermediate addition products also react with tethered alkynes and tethered aldehydes in a catalytic fashion (equations 38 and 39).[77] The stereocontrol in these processes appears to emanate from cyclic transition structures **59** and **60**, where the tethered π-system inserts into a Pd(π-allyl) intermediate.

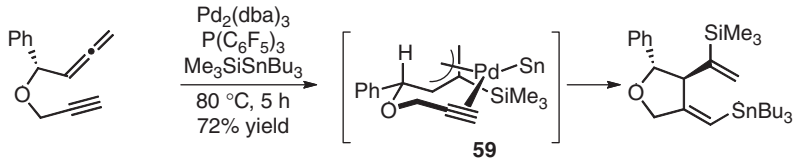


(36)

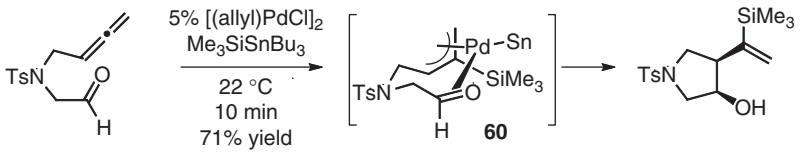


(37)

58



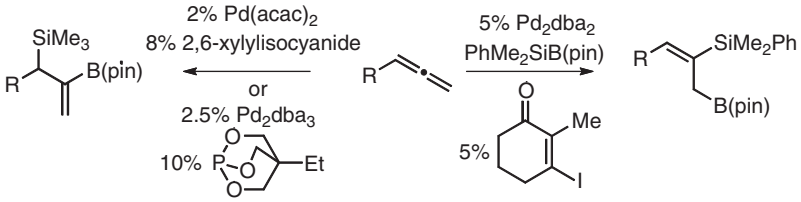
(38)



(39)

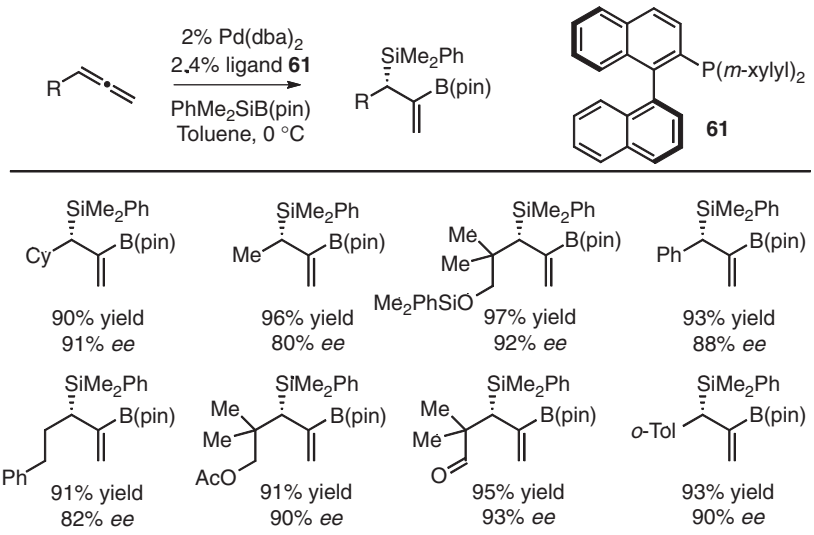
4.16.4.3 Silylboration of Allenes

The catalytic silylboration of allenes furnishes either allylboranes or allylsilanes, depending on the reaction conditions (Scheme 13).[78] Although catalysis with Pd(0) appears to proceed by a cycle A mechanism and delivers the allylsilane product, in the presence of catalytic quantities of a vinyl halide, the mechanism appears to operate by cycle B and delivers the terminal addition product. The detailed mechanism of the cycle A path to internal addition products has been studied and appears to occur by borylpalladation of the allene to give a (π-allyl)Pd(silyl) complex, which then furnishes the internal allyl silane on reductive elimination.[79]



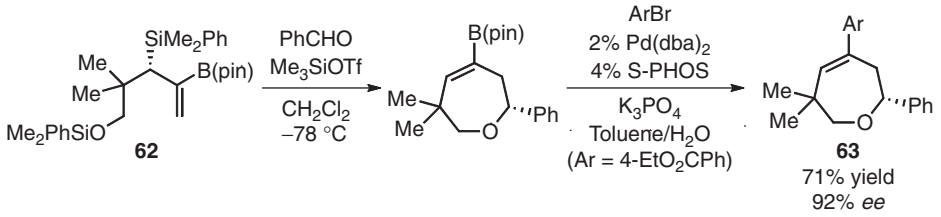
Scheme 13

The utility of the allene silylboration has been considerably expanded by the introduction of an enantioselective version of the reaction (Scheme 14).[80] High levels of selectivity are obtained with monodentate biaryl phosphine **61** and the reaction applies to a broad range of substrates. Remarkably, aldehydes are accommodated in the reaction even though (allyl)Pd intermediates are involved. The allylsilane functional group is strategically located to engage in intramolecular reactions with tethered functionality



Scheme 14

in the product. For example, compound **62** (equation 40) can engage in a Marko-type allylation, followed by cross-coupling, to deliver seven-membered ether **63** in excellent yield and diastereoselectivity.



(40)

4.16.5 Conclusion

In conclusion, the catalytic bismetallation of unsaturated hydrocarbons has advanced significantly over the past 20 years. Reagents that were once considered exotic are now commonplace and are commercially available on a large scale. Transformations that were originally examined as intriguing case studies in catalytic transition metal chemistry have developed to the point where they now provide practical solutions to important problems in stereoselective organic synthesis. Continued study of these reactions is likely to provide a stronger foundation for further design and invention of catalytic bismetallations.

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4.17 Hydroacylation of Alkenes, Alkynes, and Allenes

MC Willis, University of Oxford, Oxford, UK

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Glossary

Atom economy Is the efficiency of a chemical process in terms of all atoms involved. In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and would be 100% atom-economic.

Hydroacylation Addition of the acyl group and the hydrogen atom of an aldehyde across a C–C or C–X multiple bond. Alkenes, alkynes, and allenes are most commonly employed, generating ketone-containing products.

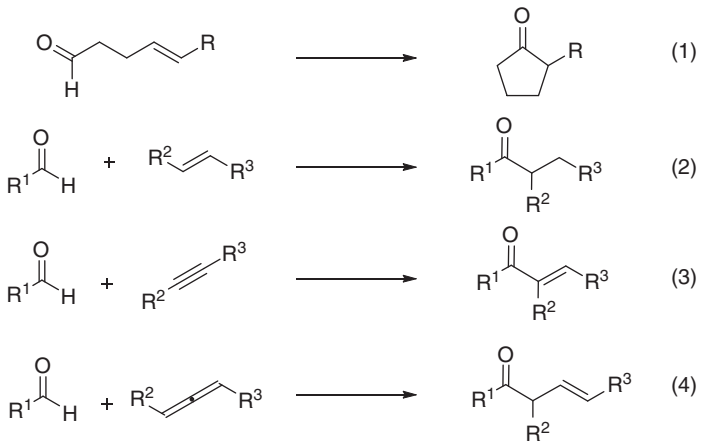
Meso compound Is an achiral diastereomer in a group of stereoisomers which also contains chiral isomers.

Organocatalytic, organocatalysis The rate of a chemical reaction is accelerated by a purely organic compound. Usually metal free reactions.

Selectivity factor(s) Is a measure of the efficiency of a kinetic resolution process. It is determined by measuring the relative rate ($k$rel) of reaction of the two enantiomers ($k$rel = $k$fast/$k$slow). It is denoted as (s), and a high (s) is usually > 15.

4.17.1 Introduction

The addition of the acyl unit and the hydrogen atom of an aldehyde across the C–C multiple bond of an alkene, an alkyne, or an allene – alkene, alkyne, and allene hydroacylation reactions, respectively – delivers synthetically useful ketone-containing products in an atom-efficient manner. Both intramolecular and intermolecular variants of these reactions are possible (Scheme 1). The most widely used and reported versions of these reactions are catalyzed by transition metal complexes, and can be traced back to the work of Sakai exploring the use of Wilkinson's complex to promote the intramolecular reaction of enals. In a key reaction, Sakai was able to convert an enal via a cycloisomerization process to generate a cyclopentanone, along with decarbonylation-derived products. The need to suppress decarbonylative side-reactions has dominated the development of rhodium-based variants of hydroacylation. Despite this challenge, the process has been advanced so that a variety of ring-sizes can be accessed using intramolecular reactions, and a broad range of substrates can be employed in intermolecular variants of the reaction. Both types of process can also be performed using asymmetric catalysts to deliver enantiomerically enriched products. Provided appropriate substrate combinations are employed, hydroacylation reactions can also be promoted by ruthenium, cobalt, nickel, and iridium complexes. Although radical-mediated versions of alkene hydroacylation predate the Sakai work, these types of reactions traditionally suffered from low efficiencies and selectivities and have been less studied than the metal-catalyzed counterparts. However, recent advances in this area have delivered synthetically useful intermolecular reactions. Recent research has also delivered both intra- and intermolecular alkene hydroacylation reactions that are catalyzed by *N*-heterocyclic carbenes (NHCs), thus providing an organocatalytic variant.



Scheme 1 Intramolecular alkene hydroacylation (equation 1), and intermolecular alkene (equation 2), alkyne (equation 3), and allene hydroacylation (equation 4).

This chapter will consider all three classes of hydroacylation – metal catalyzed, radical mediated, and organocatalytic – with the relative proportions reflecting the reported examples present in the literature. The focus is on discussing the major advances in the field, with an emphasis on reports that add to the synthetic value of hydroacylation reactions. Specific exclusions include processes based on an initial hydroformylation reaction (*see* Chapter 4.18), as well as hydrocarbamoylation and hydroesterification processes. In addition, although recent NHC-catalyzed alkene hydroacylation reactions will be considered, the extensive literature on the closely related Stetter reaction will not; this is covered in detail in Chapter 4.23. There are a number of earlier reviews on aspects of hydroacylation chemistry.[1–6]

4.17.2 Transition Metal-Catalyzed Hydroacylation

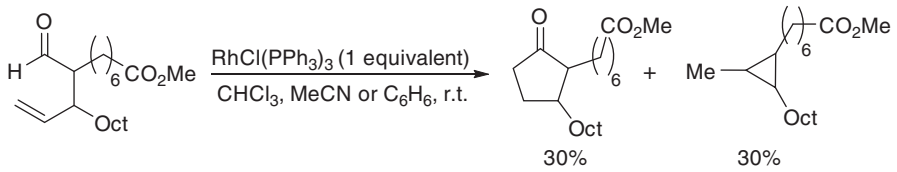
4.17.2.1 Intramolecular Alkene, Alkyne, and Allene Hydroacylation

Reports of intramolecular alkene hydroacylation reactions represent a significant body of work, and document the original discovery of the reaction, through catalyst development, applications to synthesis, and enantioselective catalysis.

4.17.2.1.1 Cyclopentanone synthesis

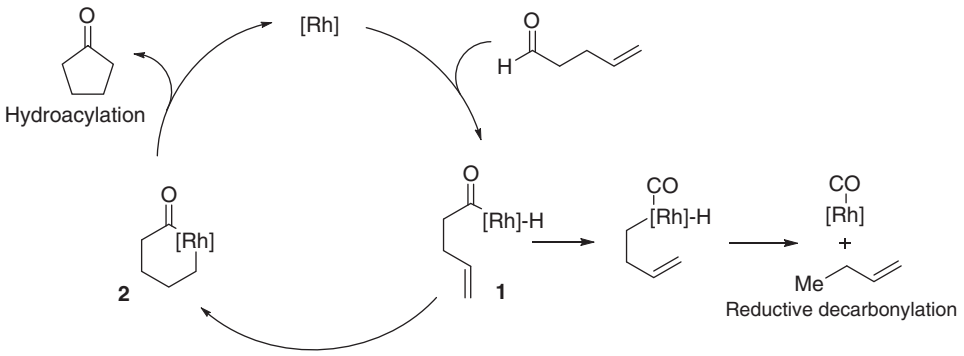
4.17.2.1.1.1 Rhodium catalysis

Sakai's 1972 report of cyclopentanone synthesis using a stoichiometric amount of Wilkinson's complex represents the first example of rhodium-catalyzed hydroacylation (equation 5).[7] The reaction also illustrates the problems of competing decarbonylative pathways, with the formation of the cyclopropane side-product occurring with equal efficiency to the desired 5-membered ketone.



(5)

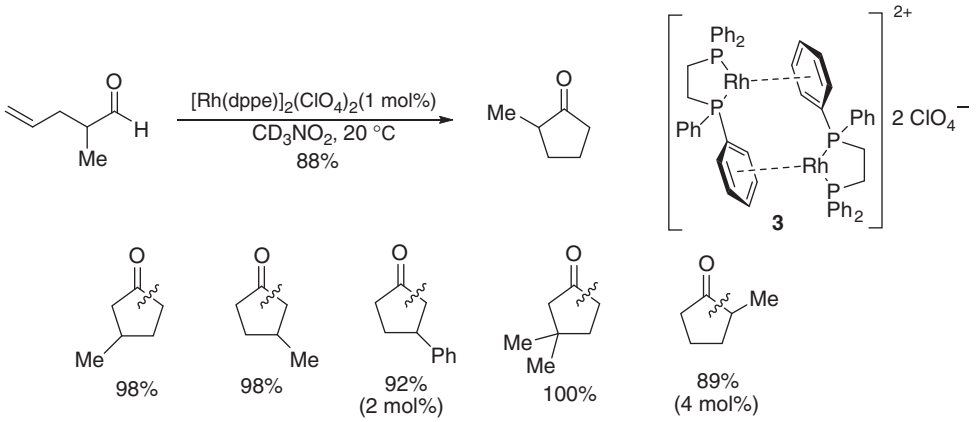
Although later reports have examined the mechanism of the intramolecular reaction in detail, it is useful to consider a simplified mechanism at this point (Scheme 2). The key steps of the mechanism involve oxidative addition of the rhodium catalyst across the aldehyde C–H bond to generate an acyl rhodium hydride **1**, subsequent addition across the alkene (**1**–**2**), followed by reductive elimination to generate a ketone product and regenerate the catalyst. The main limitation of Rh-catalyzed hydroacylation as a synthetically useful reaction stems from the general tendency of acyl-metal species, such as **1**, to undergo reductive decarbonylation. Not only does the decarbonylative process convert the starting aldehyde into the corresponding alkane, it also delivers a poorly active carbonylated catalyst. Advances in both intra- and intermolecular Rh-catalyzed processes have focused on limiting or moderating this deleterious pathway. Early structural evidence for the formation of an acyl rhodium hydride was obtained by Milstein.[8,9] The first examples of intramolecular reactions using substoichiometric amounts of rhodium were reported by Miller,[10,11] who was able to achieve modest turnovers provided that ethylene saturated chloroform was employed as a solvent. The ethylene presumably functions by blocking vacant coordination sites on rhodium and slowing



Scheme 2 Simplified mechanism for Rh-catalyzed intramolecular alkene hydroacylation.

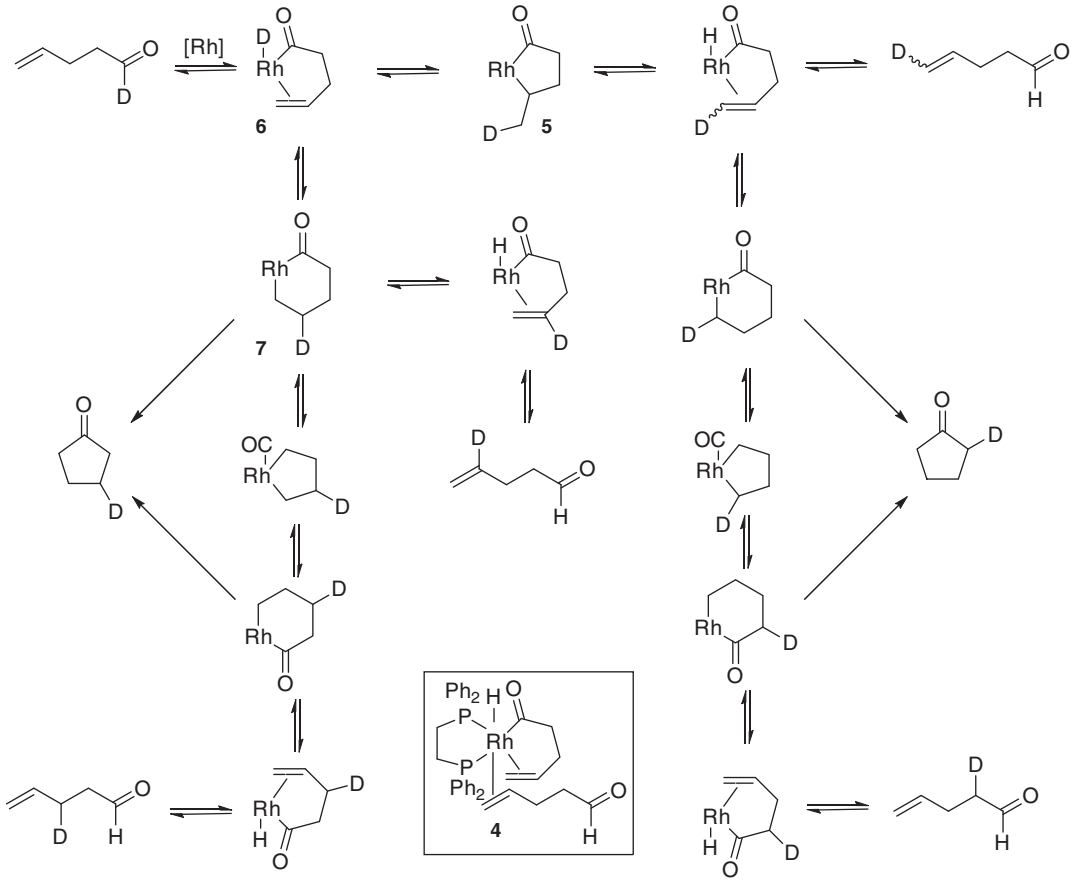
decarbonylation. Larock reported similar findings, and was also able to expand the range of cyclopentanones prepared by using modified catalysts incorporating $P(4\text{-}MeC_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$, or $P(4\text{-}Me_2NC_6H_4)_3$ as ligands.[12] Again, the use of ethylene saturated solvent was important.

A breakthrough in the development of intramolecular alkene hydroacylation chemistry was the report by Bosnich that cationic rhodium centers partnered with diphosphine ligands generated catalysts capable of delivering efficient reactions at low-catalyst loadings.[13] Bosnich evaluated a variety of (bis)phosphines and anion combinations, but settled on the use of $[Rh(dppe)]ClO_4$ as a general catalyst system. Either generating the active catalyst *in situ*, or employing the isolated dimer (**3**), allowed a broad range of substituted 4-enals to be cyclized to the corresponding cyclopentanones in good yields (**Scheme 3**). For most substrates a catalyst loading of 1 mol% delivered efficient reactions and allowed substitution at the 2-, 3-, 4-, and 5-positions of the enal substrates to be tolerated. The reactions were performed at only 20 °C. The cationic Rh-diphosphine system, as defined by Bosnich, has been the system exploited for the majority of the intramolecular hydroacylation reactions reported. Peters has reported a related zwiterionic catalyst that offered enhanced turnover frequencies,[14] and Doyle a bimetallic Ti/Rh system,[15] although neither has attracted significant further investigation.



Scheme 3 Bosnich's intramolecular alkene hydroacylation system based on cationic rhodium catalysts.

In addition to describing the first general system for intramolecular alkene hydroacylation reactions, Bosnich and coworkers also studied the mechanism of these reactions in detail.[16] Building from earlier studies by Miller, Bosnich and coworkers employed extensive kinetic and D-labeling studies to construct a mechanistic picture to account for their observations. They proposed that the low rate of decarbonylaton they observed was because of excess substrate binding to otherwise coordinatively unsaturated intermediates, generating structures such as **4** (**Scheme 4**). This correlates well with the earlier work from Miller and Larock who employed ethylene to achieve similar stabilizing effects. The Bosnich D-labeling studies resulted in extensive scrambling; the proposed mechanism that followed from these observations has every step of the process, apart from final reductive elimination, being reversible, and is summarized in **Scheme 4**. The key intermediate in this scheme is metallocyclopentane **5**, which links the two main pathways and accounts for the extensive scrambling. Final reductive elimination was proposed to be rate limiting. Recent computational studies from Morehead and Sargent broadly supports the Bosnich mechanism, but provided some refinement.[17] In particular, by studying the discrete stereoisomers of the oxidative addition product **6**, they concluded that metallocyclopentane and -hexane intermediates **5** and **7** were generated from discrete diasteromers of **6**. The computational study also supported the formation of coordinatively saturated intermediates such as **4**, but proposed that the role of the additionally coordinated substrate was to accelerate reductive elimination.



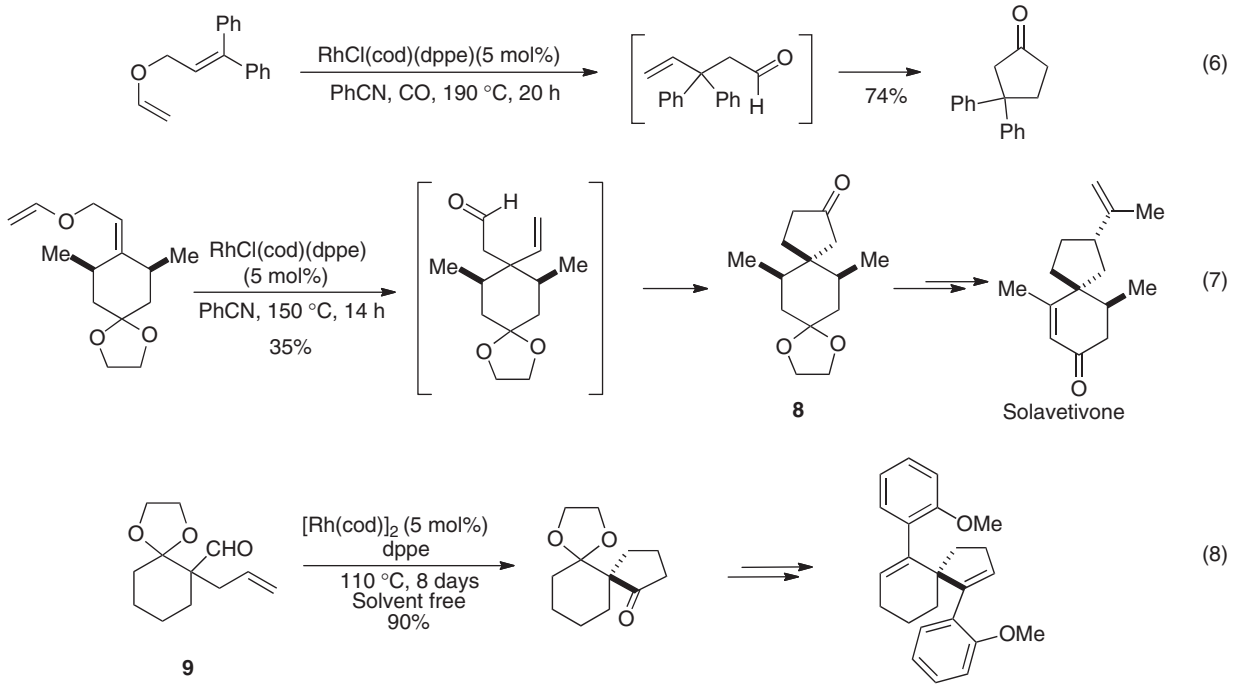
Scheme 4 Bosnich's proposed mechanism for intramolecular rhodium-catalyzed alkene hydroacylation.

The efficiency and ease of use of the rhodium-catalyzed hydroacylative formation of cyclopentanones has resulted in the methodology being applied in a number of areas. For example, rather than prepare and isolate individual enal substrates, Eilbracht demonstrated that it was possible to combine an initial Claisen rearrangement of an appropriate allyl vinyl ether with an *in situ* hydroacylative step to access cyclopentanones (equation 6; **Scheme 5**).[18] The method was not limited to relatively simple substrates, but could also be extended to more complex examples. Spirocyclic cyclopentanone **8**, a potential intermediate en route to the natural product solvetivone,[19] was prepared using a similar cascade sequence (equation 7), as were intermediates toward erythrodiene and spirojatamol.[20,21] Undheim has also utilized cyclopentanone forming hydroacylation reactions in the synthesis of spiro-compounds, and prepared a series of spirane-bridged bisarenes and spirane-bridged indenes using this chemistry. For example, enal **9**, featuring ketal functionality, was converted into the corresponding cyclopentanone in 90% yield (equation 8).[22,23]

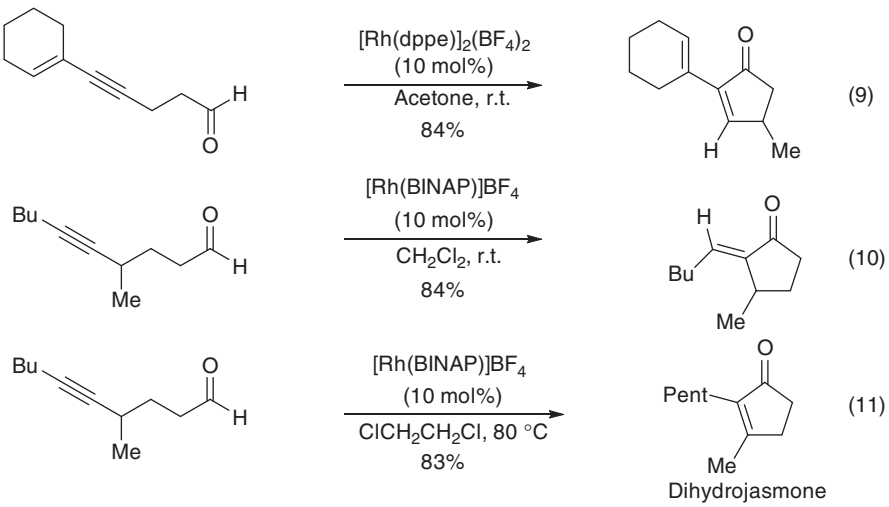
Intramolecular alkyne hydroacylation reactions are not as developed as the corresponding alkene-based processes. Fu reported the first successful method for the conversion of 4-ynals to the corresponding cyclopentenones in 2001.[24] He found that the use of the standard dppe-derived cationic Rh catalysts was efficient for these reactions and delivered a series of cyclic enones in good yields (equation 9; **Scheme 6**). An interesting feature of these reactions is that in order to achieve the desired transformations, the hydroacylative step must involve a formal *trans*-addition of the rhodium hydride across the alkyne,[25] in contrast to the normally observed *cis*-addition. Later, Tanaka was able to show that 5-ynals could be converted into *exo*-methylene cyclopentanones (equation 10).[26] Cationic Rh-systems were again employed as catalysts, this time featuring BINAP as ligand. These processes result from a conventional *cis*-addition across the alkyne. An interesting modification of this chemistry, involving simply performing the reactions at the increased temperature of 80 °C, allowed the corresponding cyclopentenone products to be obtained via a double-bond isomerization (equation 11). It was established that the isomerization was Rh-mediated.

4.17.2.1.1.2 Nickel catalysis

In 2012 Yamamoto reported the Ni-catalyzed synthesis of dihydroindenones via an intramolecular alkyne hydroacylation reaction.[27] After surveying a range of monodentate phosphine ligands the group found that $P(^{i}Pr)_3$, used in combination with Ni $(cod)_2$, generated the optimal catalyst system. Using this formulation, a range of 2-propynyl benzaldehydes were converted into the corresponding dihydroindenones (equation 12). Variation of both the alkyne terminus and the substitution pattern on

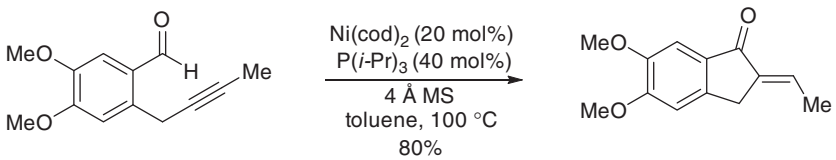


Scheme 5 Applications of rhodium-catalyzed hydroacylative cyclopentanone synthesis.



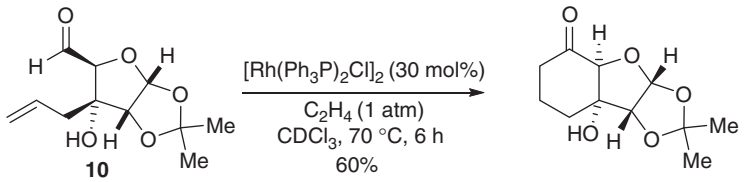
Scheme 6 Intramolecular Rh-catalyzed alkyne hydrocylation leading to 5-membered ring formation.

the arene were possible. For the more challenging examples, 20 mol% of the nickel catalyst and molecular sieves were employed. The authors proposed a mechanism which proceeds via the formation of a nickel acyl hydride intermediate.



4.17.2.1.2 Preparation of cyclohexanone and larger-ring systems

In his early work on intramolecular hydroacylation reactions, Larock noted that the preparation of ring systems other than cyclopentanones was problematic.[12] This resulted from the slower rate of cyclization associated with larger-ring synthesis, allowing decarbonylation to again become competitive. To overcome this limitation a number of strategies, mainly based on employing biased substrates, have been reported. In an early example, a carbohydrate templated enal was used to access a cyclohexanone employing Rh-catalyzed alkene hydroacylation.[28] Enal **10** was converted into the fused-ring product in a respectable 60% yield (equation 13; Scheme 7). The success of this 6-membered ring-forming process was attributed to the strain that would be present if the corresponding fused 5-membered product was generated. Sato and coworkers have reported a number of examples of dienal substrates being used to access cycloheptanones.[29,30] Their chemistry is based on an initially formed metallocyclohexanone being



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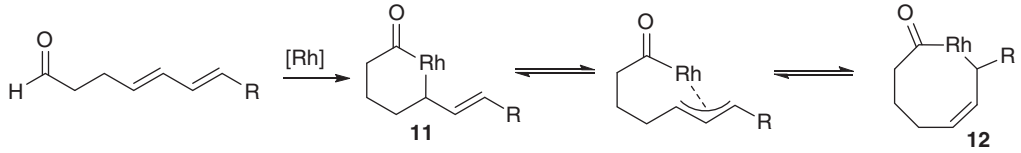

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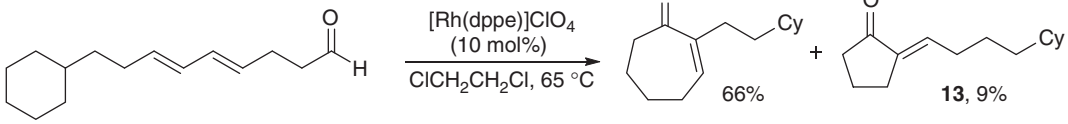


(15)

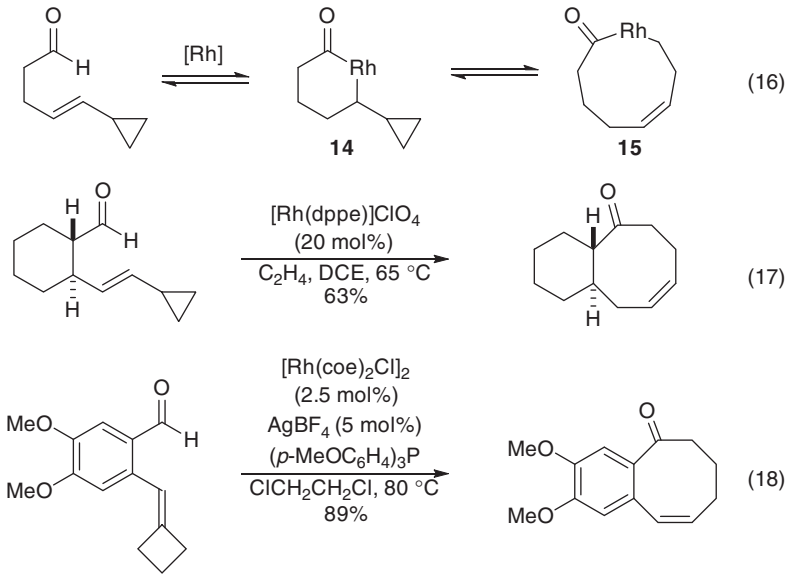
Scheme 7 Cyclohexanone and cycloheptanone syntheses using intramolecular hydroacylation.

able to equilibrate to the corresponding metallocyclooctanone by way of an allylic intermediate (**11**→**12**, equation 14). An example of a cycloheptanone-forming process is shown in equation 15; formation of cyclopentanone **13**, along with the desired 7-membered product supports their mechanistic hypothesis. Sato and coworkers have exploited their cycloheptanone methodology in a synthesis of the natural product epiglobulol.[31]

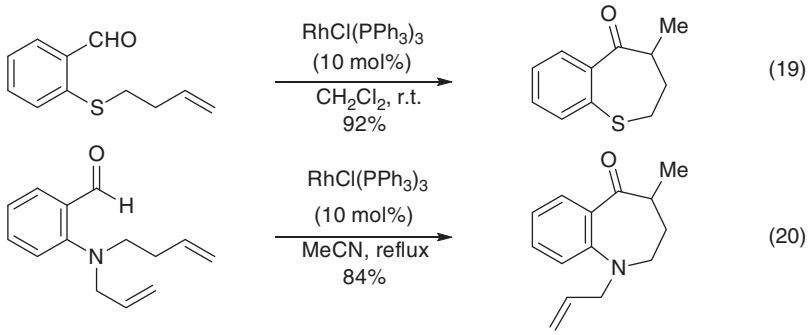
An alternative strategy to access larger-ring products involves the incorporation of small strained rings, such as cyclopropanes and cyclobutanes, into the substrates and exploiting the expansion of these strained rings to provide an entry into ring-expanded rhodacycles (for example, **14**→**15**, equation 16; Scheme 8). Shair first reported the use of cyclopropane-bearing substrates to access cyclooctanone products; in this system, cationic dppe-derived catalysts were employed to generate the 8-membered products in good yields.[32] The use of an ethylene atmosphere was found to be crucial (equation 17). Fürstner exploited related alkylidenecyclopropane substrates to access cycloheptanones,[33] and recently Aïssa has reported the use of alkylidenecyclobutane-derived substrates as an alternative route to the 8-membered systems (equation 18).[34,35] In the latter two cases, the active, cationic catalysts were generated *in situ* from the neutral diene precursors and an appropriate silver salt; notably, monodentate aryl phosphines were the ligands of choice. In an interesting extension of the cyclobutane chemistry, Aïssa was also able to utilize methylene-azetidine substrates to prepare 8-membered cyclic amines.

A final strategy to access larger-ring cyclic ketones using alkene hydroacylation involves the use of heteroatom-substituted enal substrates, such that chelation-stabilized rhodacycle intermediates will be formed. Bendorf was the first to exploit this approach, and reported the preparation of a range of medium-ring sulfur heterocycles.[36] In the optimized system, Wilkinson's complex was used to convert the sulfide-linked substrates into the corresponding cyclic ketones in good yields. Both 7- and 8-membered rings could be prepared using a range of both alkene- and alkyne-based substrates. An example transformation is shown in (equation 19; Scheme 9). Dong went on to employ a similar strategy to prepare a series of medium-ring ethers.[37] In the Dong group examples, cationic rhodium centers were partnered with chiral diphosphine ligands and delivered enantiomerically enriched products (see Scheme 13). Recently, Bendorf has studied a series of amine-based substrates;[38] Wilkinson's complex was again employed and delivered the corresponding cyclic amines efficiently (equation 20). Interestingly, an accelerating effect when employing *N*-allyl substituents (as a protecting group) was noted. Both *S*- and *N*-tethered substrates incorporating alkynes were also successfully employed, generating the corresponding *exo*-methylene medium-ring ketones.

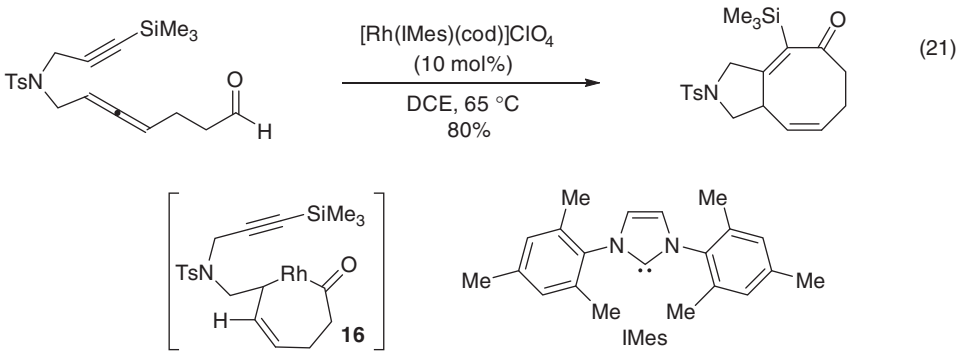
Sato and coworkers have reported the use of allene-derived substrates in an intramolecular hydroacylative-route to 8-membered ketones.[39] In their approach, the combination of an initial intramolecular hydroacylative step, to generate a key 7-membered rhodacycle (i.e., **16**; Scheme 10), is combined with an intramoleculer addition to a tethered alkene or alkyne to generate the desired medium-ring systems. An example is shown in equation 21; the use of a cationic rhodium center partnered



Scheme 8 Ring expansion strategies to 8-membered ketones.



Scheme 9 Chelation-controlled strategies to medium-ring ketones.



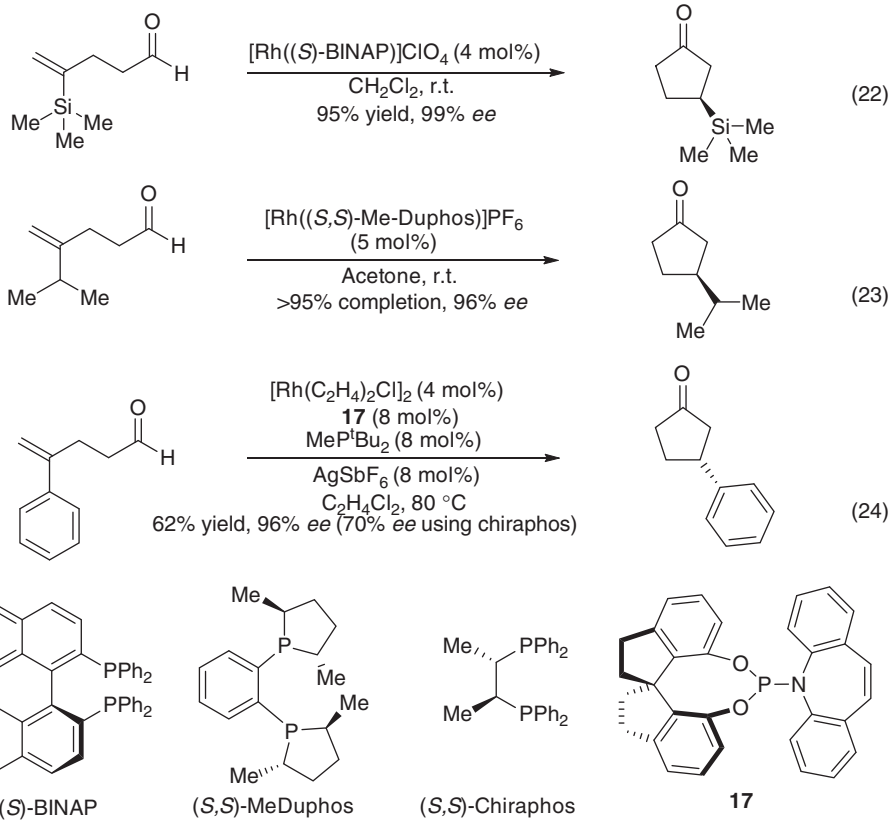
Scheme 10 Intramolecular allene hydroacylation en route to 8-membered ketones.

with an NHC-ligand was found to be optimal. The process was tolerant of both tethered alkynes and alkenes, and represents a formal [6+2] cycloaddition of 4-allenals with alkynes.

4.17.2.1.3 Enantioselective intramolecular reactions

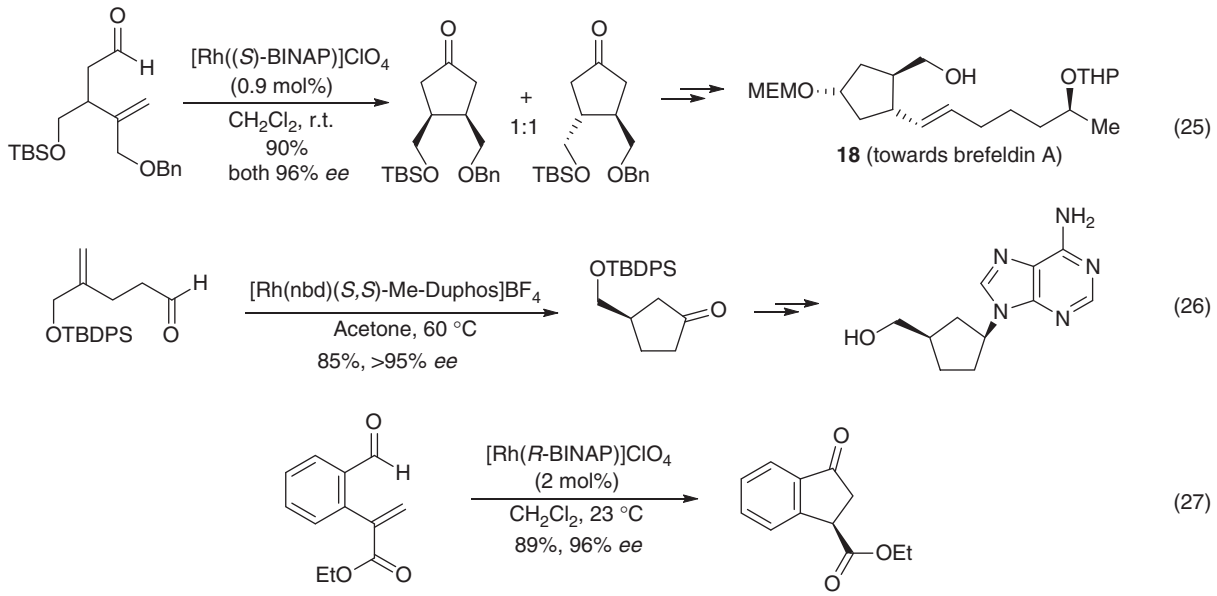
The attractive goal of a catalytic asymmetric synthesis of cyclopentanones, partnered with the observation that the most general catalysts for achiral intramolecular hydroacylation reactions are all based on a cationic rhodium center used in combination with a

diphosphine ligand, has resulted in significant effort in this area. Simply exchanging the achiral ligands used in the earlier chemistry for enantiomerically enriched equivalents has allowed a wide range of catalysts to be explored. Early work in this area from Sakai and coworkers employed neutral rhodium catalysts, and by using high catalyst loadings (25 mol%) they were able to produce cyclopentanones with moderate to good *ee*s (typically 75%).[40] Both Sakai,[41] and later Bosnich,[42–44] established that the use of cationic rhodium complexes partnered with chiral diphosphines could deliver extremely selective reactions. Bosnich evaluated a range of diphosphine ligands and found a significant degree of substrate specificity for the cyclization of 4-enals. For example, BINAP was most effective for substrates with tertiary alkyl or ester substituents (equation 22; **Scheme 11**), whereas DuPhos was most selective for primary and secondary alkyl groups (equation 23). Aryl-substituted substrates were only moderately selective (70–75% *ee*) using a variety of diphosphine-derived catalysts. However, Carreira has recently shown that the use of hybrid alkene-phosphoramidate ligands allows aryl-substituted substrates, generating 2-aryl cyclopentanones, to be employed with high enantioselectivity.[45] For example, the parent Ph-substituted substrate delivered the corresponding cyclopentanone with 96% *ee* (equation 24). The equivalent transformation incorporating the ligand chirophos delivered material of only 78% *ee*.[42] A notable feature of the Carreira reaction system was the incorporation of an achiral coligand (in this case MeP^tBu_2); the identity of these coligands was shown to dramatically affect both the efficiency and selectivity of the reactions.



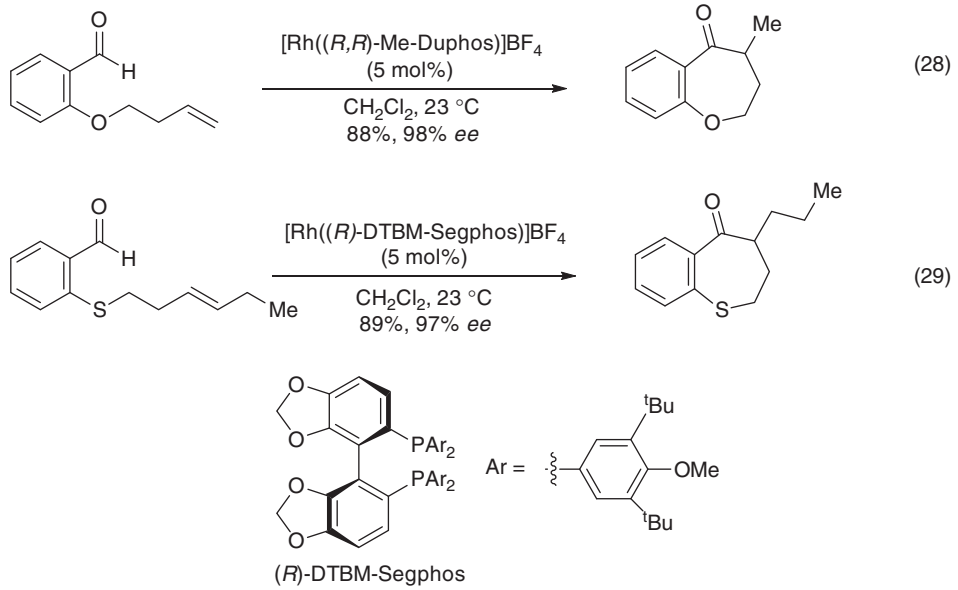
Scheme 11 Enantioselective intramolecular hydroacylation for cyclopentanone synthesis.

The relatively low-catalyst loading and high selectivities achieved in these cyclization reactions has resulted in a number of interesting applications. Rousseau and Mioskowski employed a kinetic resolution using a cationic rhodium complex in a formal synthesis of brefeldin A;[46] the use of Rh[(*S*)-BINAP]ClO_4 (0.9 mol%) as the catalyst triggered an intramolecular hydroacylation reaction to deliver a 1:1 mixture of the diastereomeric target cyclopentanones in high *ee* (equation 25). The *trans*-configured product was advanced through a short sequence to deliver alcohol **18**, an intermediate in the synthesis of brefeldin A previously reported by Gais.[47] A Me-DuPhos containing catalyst was employed by Castillón in the enantioselective synthesis of carbocyclic nucleosides (equation 26).[48] The key hydroacylative step delivered the desired cyclopentanone with >95% *ee*. Sakai and coworkers have explored a number of applications of enantioselective cyclizations, including the preparation of spiro[4.4]nonanedione derivatives using two sequential hydroacylations.[49,50] Sakai and coworkers have also explored the use of intramolecular hydroacylation in enantioselective desymmetrization reactions to deliver disubstituted cyclopentanone products.[51] Morehead has extended the use of enantioselective intramolecular hydroacylation to the synthesis of enantiomerically enriched 3-substituted indanones.[52] Optimization revealed BINAP-derived catalysts to be most effective, and a variety of 3-substituted products could be obtained in high yield with excellent *ee* (equation 27; **Scheme 12**).



Scheme 12 Applications of enantioselective intramolecular hydroacylation reactions.

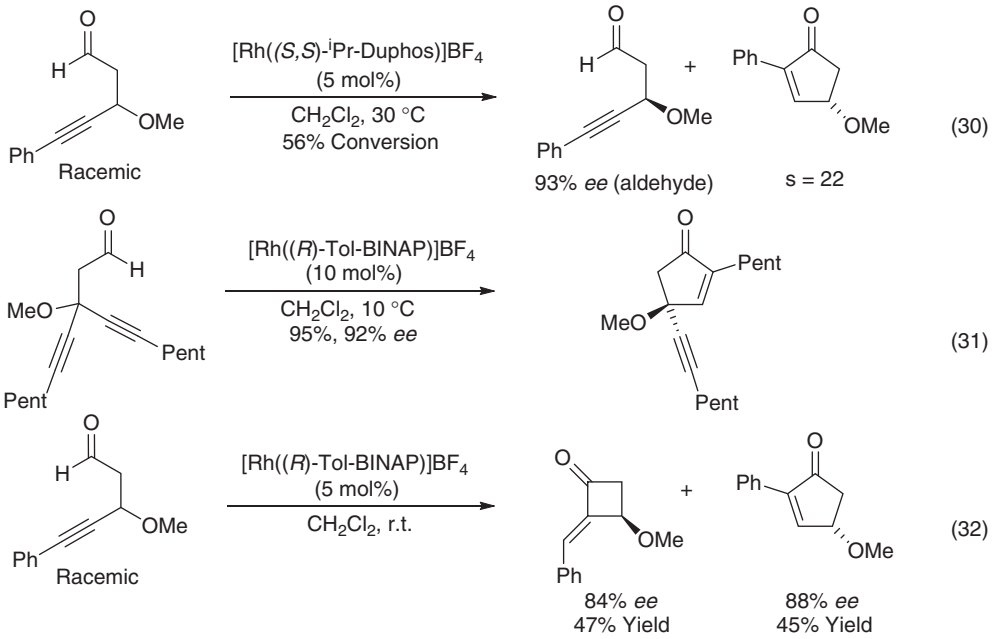
Dong and coworkers have exploited chelation-control intramolecular hydroacylation reactions to develop enantioselective routes to a number of medium-ring systems. Using substrates related to those reported by Bendorf (see Scheme 9), Dong and coworkers were able to prepare a range of *O*- and *S*-substituted 7- and 8-membered ketones efficiently and selectively (Scheme 13).[37] Ligand choice was somewhat substrate dependent, however, excellent substitution tolerance was demonstrated, allowing access to 2- and 3-substituted products (equations 28 and 29). The authors also reported an interesting regiochemical switch based on ligand choice, in an achiral substrate, whereby the choice of ligand allowed selection of the ring-size of the product. A related approach has also been described for the synthesis of medium-ring lactones using intramolecular ketone hydroacylation.[53]



Scheme 13 Enantioselective synthesis of *O*- and *S*-linked medium-ring ketones. Absolute stereochemistry of products not provided.

Although alkyne hydroacylation does not result in the creation of a stereogenic center, the use of racemic-chiral, achiral, or *meso* substrates allows the exploration of enantioselective reactions via kinetic resolution or desymmetrization pathways. Fu has studied the cyclization chemistry of 4-alkynals using both of these concepts. For example, treatment of a range of racemic 4-alkynals with an asymmetric rhodium catalyst affected efficient resolution to deliver enantiomerically enriched cyclopentanones in good

yields.[54] The example shown in equation 30 is typical, and illustrates the use of two-point binding substrates, needed to achieve the desired selectivity. Selectivity factors (s) of 20–40 could be achieved, allowing either the unreacted starting material or cyclized product to be obtained with high levels of stereo-induction. Achiral substrates bearing a quaternary center were employed in desymmetrization reactions. The use of Tol-BINAP-derived catalysts allowed enantiomerically enriched cyclopentenones to be obtained with high levels of selectivity in good yield; an illustrative example is shown in equation 31. The final example shown in (equation 32; Scheme 14) is a rare example of a catalytic parallel kinetic resolution.[55] Treating racemic 4-alkynals with a Tol-BINAP-derived Rh-catalyst delivered both the cyclopentanone and *exo*-cyclobutanone, both with high *ee*. As with the simple kinetic resolution and desymmetrization chemistry, a methoxy-substituent was needed to ensure high selectivity.



Scheme 14 Enantioselective alkyne-based transformations.

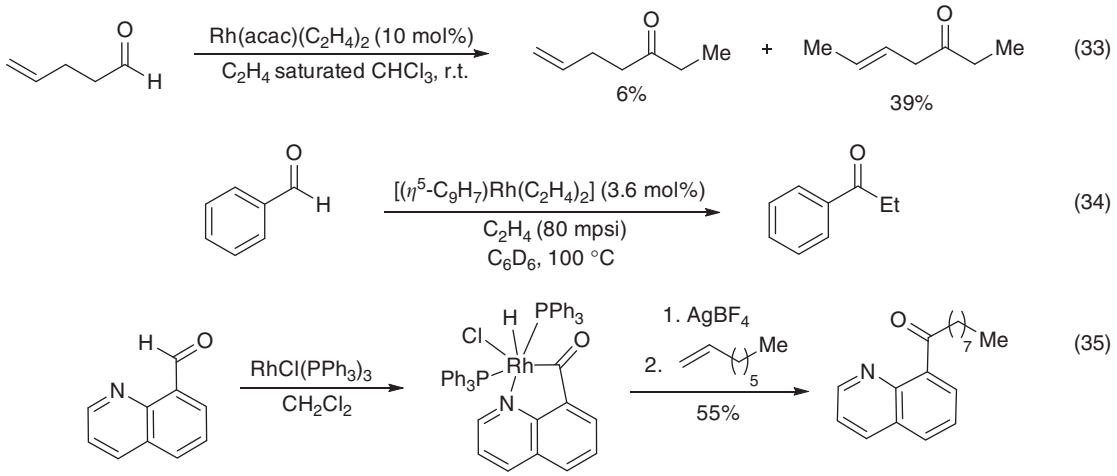
4.17.2.2 Intermolecular Alkene, Alkyne, and Allene Hydroacylation

Unlike the corresponding intramolecular chemistry, intermolecular hydroacylation is not limited to the use of only rhodium catalysts. Although rhodium-based reactions represent the majority of examples, there are notable processes based on ruthenium, cobalt, iridium, and nickel. These will be considered in order.

4.17.2.2.1 Rhodium catalysis

The challenges that limited the extension of rhodium-catalyzed intramolecular hydroacylation reactions beyond cyclopentanone synthesis are even more pronounced for intermolecular reactions. The dominant strategy to limit reductive decarbonylation has been the use of chelation control, although a small number of alternative approaches have been described. The first report of rhodium-catalyzed intermolecular hydroacylation came from Miller,[10,56] and followed from his intermolecular studies. He found that when the catalyst for a proposed cyclization was exchanged from Wilkinson's complex to $Rh(acac)(C_2H_4)_2$ the products from the intermolecular hydroacylation reaction with ethylene were isolated (equation 33). For example, reaction of pentenal with $Rh(acac)(C_2H_4)_2$ in ethylene saturated chloroform provided a mixture of heptenones, with the *E*-hept-5-en-2-one as the major component in 39% yield. Cyclopentanone was detected in only 1% yield. Reactions with saturated aldehydes provided no hydroacylation adducts, however, 4-hexenals were successfully employed. Vora was also able to show that *Z*-4-heptenal could be combined with ethylene, using identical conditions, to deliver 6-nonen-3-one in a 26% yield.[57] The requirement for the aldehydes to contain an alkene unit suggested that internal alkene coordination was a prerequisite for reactivity, and represents the first example of chelation-controlled intermolecular hydroacylation. Milstein reported an early nonchelating system based on the use of indenyl-rhodium complex $[Rh(h^5\text{-}C_9H_7)(C_2H_4)_2]$, to catalyze the addition of aromatic aldehydes to ethylene (equation 34).[58] By using relatively high pressures of ethylene (1000 psi at 25 °C) it was possible to achieve turnover numbers of approximately 4 h^{-1}. The early Miller chemistry had shown that a pendant alkene was capable of providing some stabilization, thus limiting

decarbonylation; Suggs extended this concept and was the first to use heteroatom coordination to control intermolecular hydroacylation chemistry, a strategy that has delivered the majority of effective rhodium-based processes.[59–61] The early Suggs chemistry was based on the use of 8-quinoline carboxaldehyde and the observation that when combined with Wilkinson's complex a stable acyl rhodium hydride was generated (equation 35). Treatment of this complex with a silver salt and an alkene resulted in the products of intermolecular hydroacylation, albeit in a stoichiometric manner. Attempts to employ substoichiometric Wilkinson's complex were unsuccessful (**Scheme 15**).



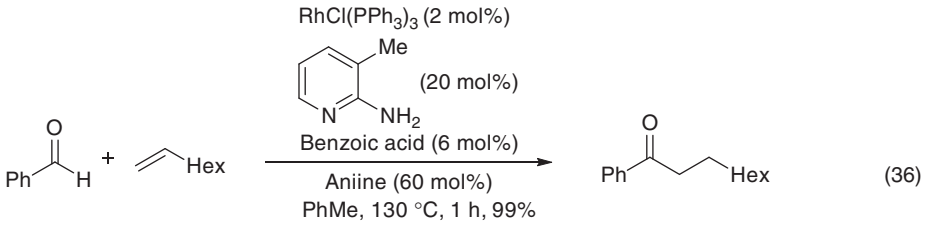
Scheme 15 Early intermolecular rhodium-catalyzed alkene hydroacylation.

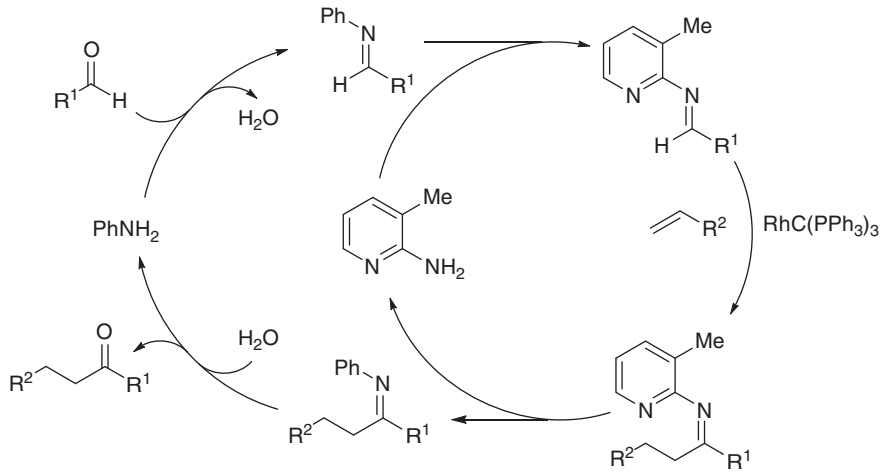
Remaining with *N*-chelation as the mode of control, Jun found that the use of *in situ* generated picolyl imines could serve as chelating aldehyde equivalents.[62] Although Suggs had previously shown that isolated imines similar to **19** could generate stable rhodium hydride complexes,[63–65] the realization that the required imines could be generated *in situ* represented a considerable advance. The optimized catalyst system involved treating a mixture of the aldehyde and the alkene with Wilkinson's complex (2 mol%), picolyl amine (20 mol%), benzoic acid (6 mol%) and aniline (60 mol%) in toluene at 130 °C (equation 36).[66] Using this method a varied range of alkenes and aldehydes could be combined in good to excellent yields. Heteroaromatic aldehydes,[67] and electron-poor alkenes, such as enoates could also be employed as substrates.[68] The proposed mechanism is shown in **Scheme 16**, and illustrates the transimination process established from the use of aniline and benzoic acid as cocatalysts (along with Wilkinson's complex and 2-amino-3-picoline). Although the original system was very effective for aryl aldehydes, a modification, introducing cyclohexylamine and *p*-trifluoromethylbenzoic acid, was needed to allow the efficient use of alkyl aldehydes, which were plagued by the formation of aldol-derived side-products.[69]

In creative extensions of their chemistry, Jun and coworkers have shown that it is possible to achieve the same type of intermolecular reactivity commencing from either allyl alcohols or simple alcohols (**Scheme 17**). Allyl alcohols are employed with the same basic catalyst system, and following an *in situ* isomerization to the aldehyde, deliver the products of hydroacylation in good yield (equation 37).[70] The use of simple alcohols as substrates requires the addition of a sacrificial alkene, needed to allow initial rhodium-catalyzed alcohol to aldehyde oxidation, before entering the catalytic cycle as described previously (equation 38).[71] Rather than employ preformed Wilkinson's complex, a mixture of $RhCl_3$ and triphenylphosphine was employed as catalyst. Related chemistry describing the use of primary amines as aldehyde equivalents,[72] and the use of methanol as a formaldehyde equivalent,[73] has also been described. Recent work has focused on the use of a number of related strategies to aid in catalyst support and recycling.[74,75] Kim and Leehave reported the use of the basic Jun chemistry in their synthesis of the indolizidine alkaloids (–)-167B and (–)-209D.[76]

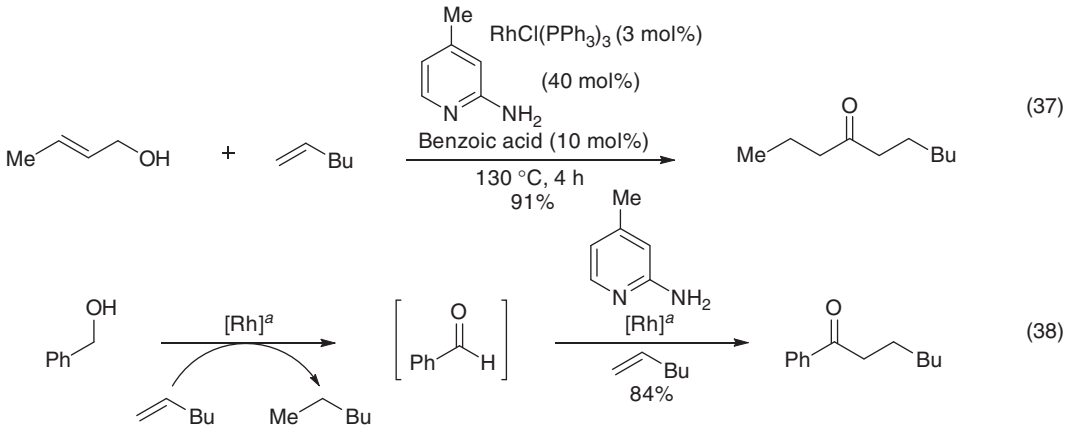
In an attempt to improve the efficiency and to address the high loading of aminopicoline cocatalysts often needed in the Jun chemistry, Breit and coworkers have reported the design and application of a bifunctional catalyst system.[77] Rather than using a rhodium center partnered to a phosphine with additional aminopicoline as a cocatalyst, the Breit system employs a bifunctional aminopicoline-phosphine ligand (equation 39). Using this approach, 5 mol% of $[Rh(cod)BF_4]_2$ in combination with 10 mol% of aminopicoline-phosphine **20**, promoted efficient intermolecular hydroacylation between a range of aryl aldehydes and simple alkenes (equation 39). Although the amounts of rhodium catalyst employed are similar to the Jun chemistry, no additional aminopicoline was needed. This bifunctional catalyst system was also successfully applied to the preparation of indanones by the cyclization of the corresponding stryl-aldehydes (see equation 27 for related reactions) (**Scheme 18**).

Jun and coworkers have applied their catalytic rhodium/aminopicoline methodology to the intermolecular hydroacylation of alkynes.[78] The catalytic system generated from Wilkinson's complex, 2-amino-3-methylpicoline and benzoic acid was effective for





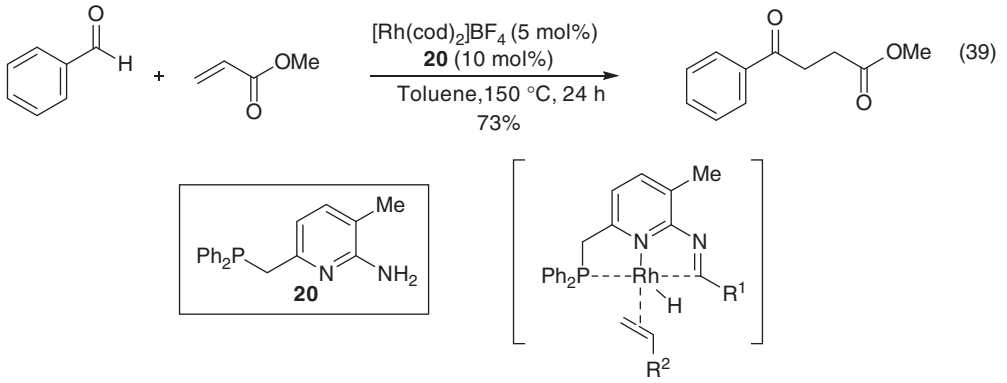
Scheme 16 Catalytic intermolecular alkene hydroacylation using catalytic aminopicoline.



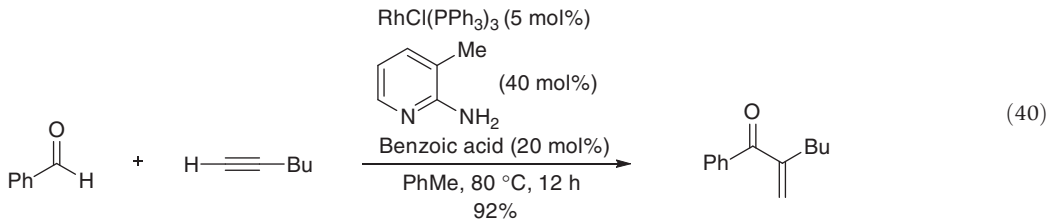
[a]$RhCl_3 \cdot H_2O$ (3.3 mol%), PPh_3(16.5 mol%), 2-amino-4-picoline (100 mol%), PhMe, 130 °C.

Scheme 17 Allylic alcohol and simple alcohol starting materials in intermolecular hydroacylation reactions.

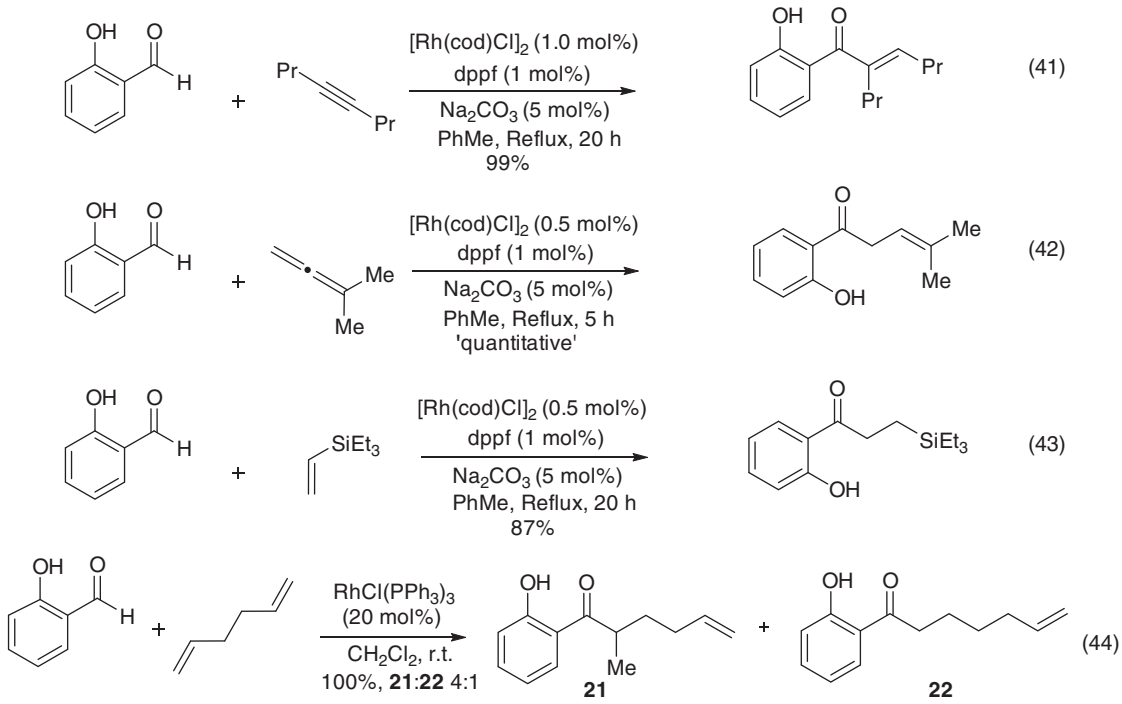
the combination of aryl and alkyl aldehydes with terminal alkynes (equation 40). Interestingly, the dominant products in the majority of examples studied were branched α,β-enones. Selective formation of the linear isomers was only possible with the use of alkynes-bearing sterically demanding substituents in combination with alkyl aldehydes. This selectivity for branched products was unique when reported. Castillón has recently shown that greater quantities of the linear adducts can be obtained in the Jun system by the use of bulkier phosphine ligands.[79] Jun has also applied his Rh/picoline catalyst system to alkyne-cleavage/hydroacylation processes.[80]



Scheme 18 Breit's bifunctional catalyst system for intermolecular hydroacylation.



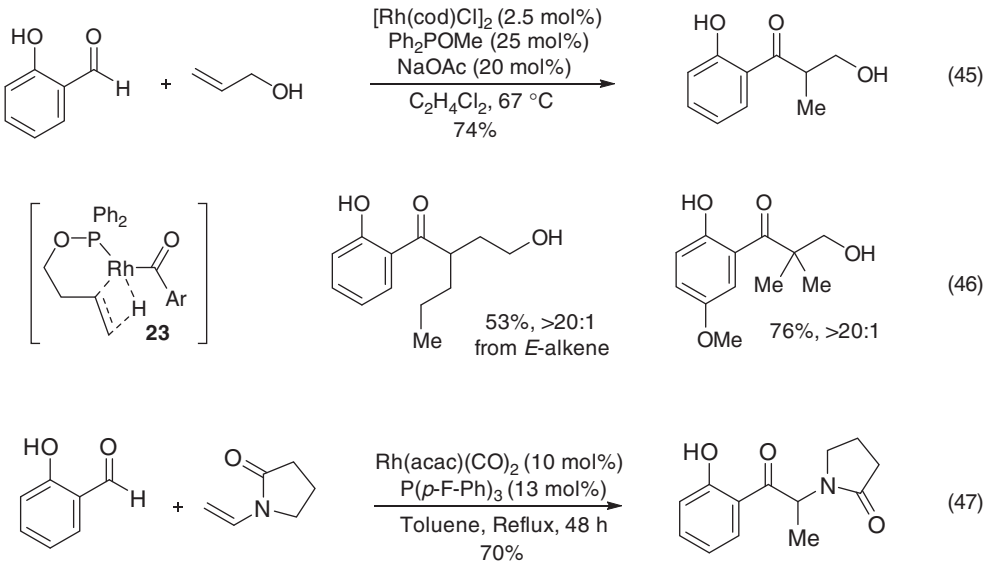
One of the most favored chelation-modes to stabilize acyl rhodium hydride intermediates is that generated from anionic salicylaldehyde derivatives. Initially reported by Miura, salicylaldehyde could be combined with alkynes, simple allenes, and vinyltrimethylsilane (equations 41–43; **Scheme 19**).[81,82] This initial report used a catalyst generated from $[Rh(cod)Cl]_2$ and dppf, with Na_2CO_3 as a base, in refluxing toluene. Although limited in alkene scope, a range of alkynes substrates were successfully employed. Suemune extended the chemistry to include reactions with diene substrates, and observed that using Wilkinson's complex under mild conditions (CH_2Cl_2, room temperature) delivered excellent product yields, although regiochemical mixtures were obtained (equation 44).[83,84] However, modification of the catalyst allowed the selective production of either regioisomer; the use of $[RhCl(coe)_2]_2$, P(*o*-MePh)$_3$, $AgClO_4$, and NaOAc delivered the linear isomer, whereas the use of $[RhCl(coe)_2]_2$ in



Scheme 19 Salicylaldehye as a substrate in rhodium-catalyzed alkene, alkyne, allene, and diene hydroacylation.

combination with $NH(^iPr)_2$ as base, produced the branched isomer. The authors propose a mechanistic scenario in which a chelating acyl rhodium hydride is combined with chelated diene component.

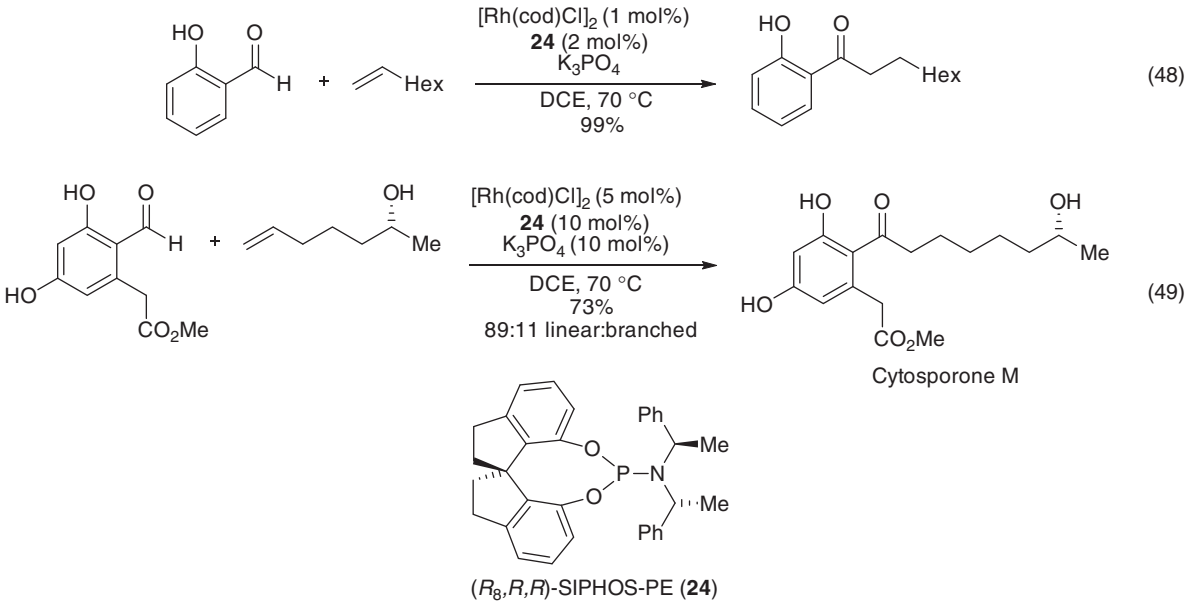
Recent work from Dong and coworkers has considerably extended the utility of salicylaldehyde-based hydroacylation chemistry, allowing the production of a host of synthetically useful products from variation of the C–C multiple-bond coupling partner. For example, Dong and coworkers demonstrated that the use of homoallylic alcohol substrates delivered homoaldol products.[85] Key to success in this chemistry was the use of a cooperative catalyst system in which a rhodium catalyst was combined with a phosphinite catalyst, to allow simultaneous binding of the alcohol and the metal center (see intermediate **23**). In the optimized system, ($[Rh(cod)Cl]_2$) was used in combination with methyl diphenylphosphinite (Ph_2POMe) and NaOAc. Using these conditions it was possible to combine a broad range of salicylaldehyde derivatives with diverse homoallylic alcohols (equation 45; **Scheme 20**). 2-Hydroxystyrenes were also shown to be competent substrates. Dong and coworkers subsequently reported the application of the same cooperative catalyst system to the hydroacylation of allylic alcohols, leading to the formation of aldol products.[86] Using an almost identical reaction system, it was possible to combine a variety of salicylaldehyde derivatives with a range of allylic alcohols (equation 46). It was possible to employ both 1,2- and 1,1-disubstituted alkenes, leading to the formation of products featuring tertiary and quaternary centers, respectively. Taken together, these two studies show that both aldol and homoaldol products are accessible using intermolecular alkene hydroacylation chemistry. In related chemistry, focused on extending the variety of alkene components that can be employed in hydroacylation chemistry, Bolm and Zhang have combined *O*-chelating salicylaldehydes with enamide substrates to access *α*-amido ketones in a single step.[87] A catalyst system comprising $[Rh(acac)(CO)_2]$ and $P(p\text{-F-Ph})_3$, used in refluxing toluene, delivered exclusively the branched adducts in good yields (equation 47).



Scheme 20 Homoallylic and allylic alcohols, and enamides as hydroacylation substrates.

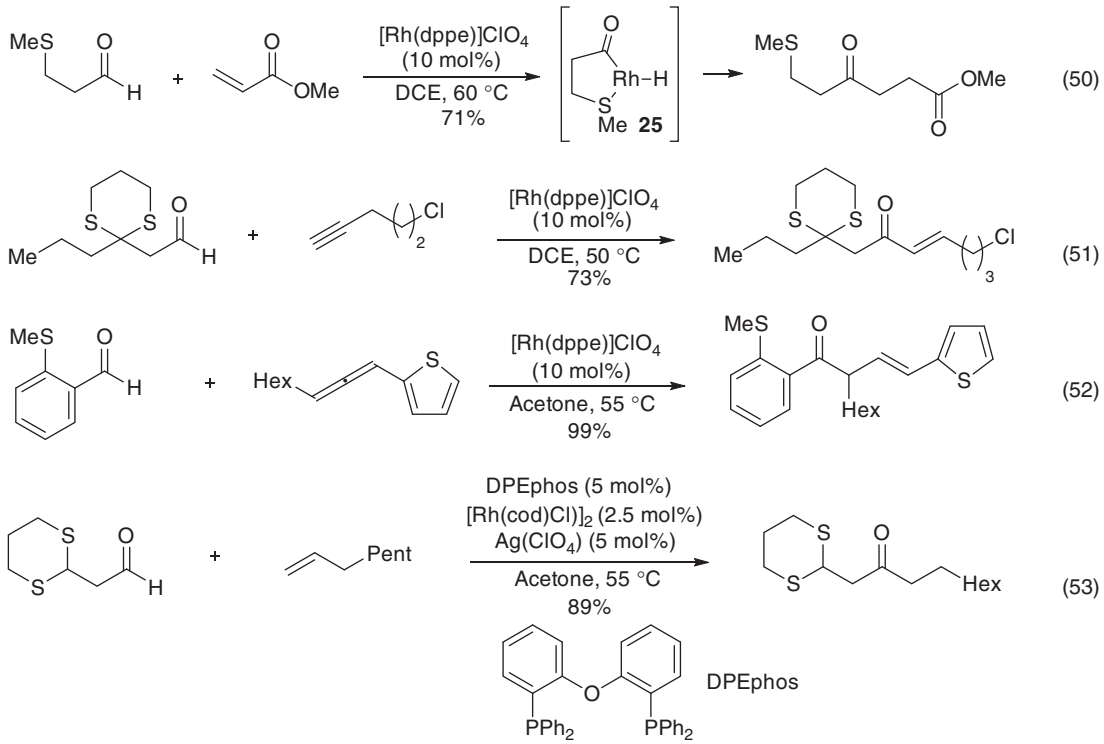
Dong and coworkers have employed a salicylaldehyde-based alkene hydroacylation strategy to achieve the successful total synthesis of eight members of the octaketide natural product family.[88] To achieve the required high levels of linear selectivity required for the synthesis, Dong and coworkers have developed the use of a chiral phosporamidate ligand. The use of this ligand system also allowed the reactions to be achieved with Rh-loadings of only 2 mol%. The optimized reaction system combines $[Rh(cod)Cl]_2$, phosphoramidate **24** (SIPHOS-PE) and K_3PO_4, in dichloroethane at 70 °C, and was effective for an impressive range of alkenes bearing diverse functional groups (**Scheme 21**). Although DCE was established as the optimal solvent, the authors were able to demonstrate that tetrahydrofuran, 1,4-dioxane, and 2-methyltetrahydrofuran were also viable solvents for the reactions. A biphasic DCE/water solvent system could also be employed. To achieve the fragments needed for the proposed octaketide synthesis, a range of chiral alcohol-bearing terminal alkenes were employed as substrates (for example, see equation 49), and delivered the natural products directly from the hydroacylation reaction. A detailed mechanistic study using D-labeled aldehydes and alkenes was also performed; conclusions from the study were that branched hydride insertion was fast and fully reversible, and that linear hydride insertion was fully irreversible for activated alkenes such as styrene and *tert*-butyl acrylate, and largely irreversible for unactivated alkenes such as 1-hexene. Hydride insertion was proposed to be turnover limiting for the linear pathway (equations 48 and 49).

S-Substituted aldehydes have proven to be an equally popular class of substrates for rhodium-catalyzed chelation-controlled hydroacylation reactions. Following on from Bendorf's intramolecular examples,[36] Willis demonstrated that *β*-*S*-substituted aldehydes were competent substrates for intermolecular alkene and alkyne hydroacylation.[89–91] Using a simple dppe-derived



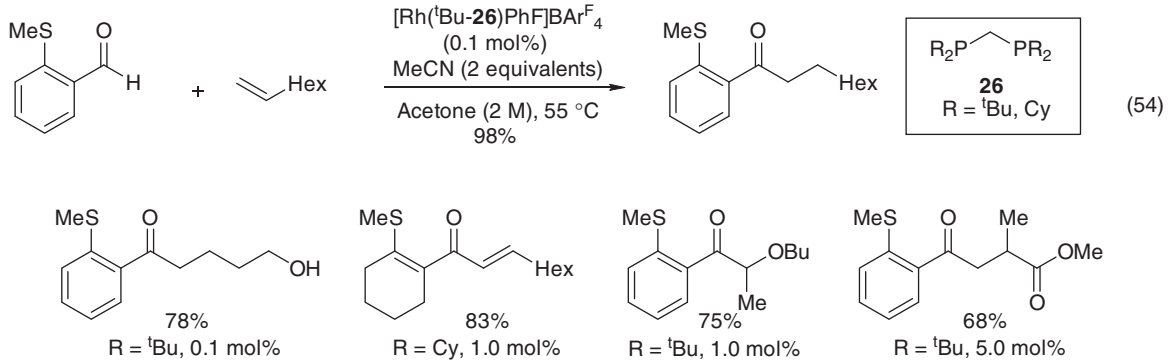
Scheme 21 Salicyladehydes as substrates for octaketide synthesis.

cationic rhodium catalyst, the group was able to show that, provided the *S*-substituent was located β to the carbonyl, allowing formation of a 5-membered chelate (**25**), it was possible to have significant variation in the structure of the C–C multiple-bond coupling partner. Alkyl and aryl aldehydes as well as dithiane-substituted examples could also all be successfully employed (Scheme 22, equations 50–51). Mono-, di-, and tri-substituted allenes were also shown to be good substrates, with reaction generally occurring at the least hindered C=C, delivering nonconjugated enone products (equation 52).[92] The initial work was followed up by the development of an improved catalyst system based on the hemilable ligand DPEphos. Using this modified catalyst, the group was able to expand the range of alkenes that could be employed, and in particular, less active simple terminal alkenes such as 1-octene could be used efficiently (equation 53).[93]



Scheme 22 β-*S*-Chelating aldehydes in rhodium-catalyzed alkene, alkyne, and allene hydroacylation.

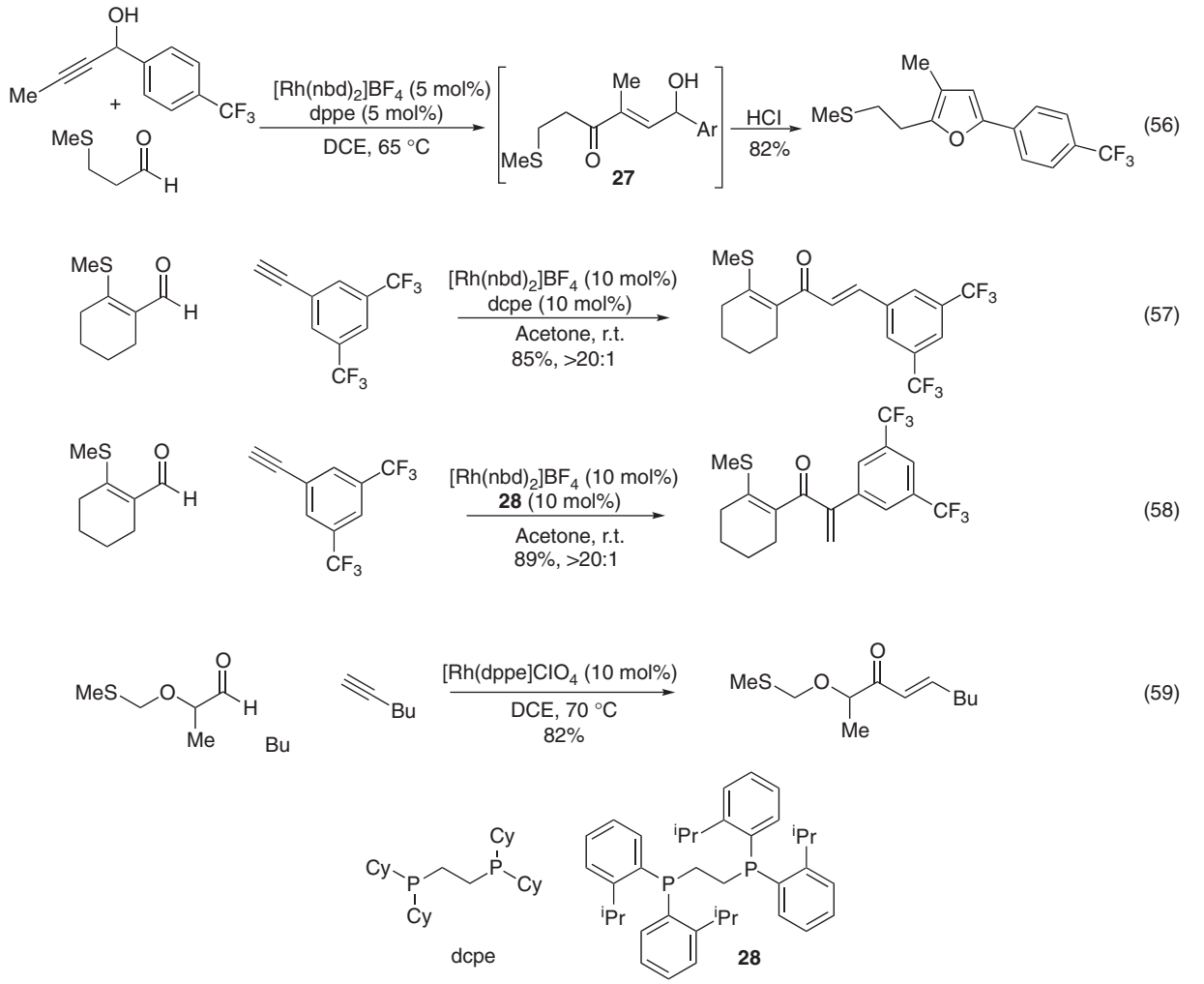
Recently, Weller and Willis have reported a further advance in catalyst design for rhodium-catalyzed intermolecular hydroacylation reactions. Employing small bite-angle diphosphines ($R_2PCH_2PR_2$), initially developed by Hoffmann, they were able to achieve alkene hydroacylation reactions with catalyst loadings as low as 0.1 mol%.[94] To achieve these low-catalyst loadings, it was necessary to perform the reactions at high concentrations (2 M), and to employ a small amount of MeCN as an additive (equation 54). The ^{t}Bu-variant of the ligand was shown to be most effective for alkene substrates, with the Cy-version being optimal for alkynes. These highly active catalysts also allowed the range of alkene-based substrates to be increased. For example, 1,1- and 1,2-disubstitted alkenes could be employed, as could simple enol ethers. Related ligand systems based on a R_2P-N(Me)-PR_2 framework have also been shown to generate highly active catalysts for alkyne systems.[95] In an interesting extension of this chemistry, the same groups have been able to combine an initial Rh-catalyzed hydroacylation process with a Rh-catalyzed methyl sulfide reduction step. Using the small bite-angle catalyst systems, the same complex was shown to promote both the hydroacylation step and a reduction step using a silane reductant (H-Si(OEt)$_3$). The result of this cascade process is a 'traceless hydroacylation' in which the ultimate product does not feature the initial chelating *S*-substituent (equation 55; **Scheme 23**).[96]



Scheme 23 Small bite-angle phosphines in hydroacylation reactions and 'traceless hydroacylation.'

The reliability of the *β*-*S*-chelation motif has allowed applications of the chemistry to be developed. For example, employing propargylic alcohols as substrates delivers enone-allylic alcohol products (**27**) that are suitable for direct conversion to substituted furans.[97] The use of a dppe-derived catalyst allowed the use of a range of aryl- and alkyl aldehydes, together with a variety of substituted alkynes; work-up of the reactions with weak acid delivered the furan products directly (equation 56). Remaining with alkyne hydroacylation, Weller and coworkers have shown that it is possible to achieve a ligand-controlled switch between linear and branched-selective reactions.[98,99] If aryl aldehydes were employed, electron-rich small bite-angle ligands generated highly linear-selective reactions (equation 57). Conversely, the use of a dppe-derived ligand featuring *ortho*-^{i}Pr groups (**28**), delivered branched-selective transformations (equation 58). Willis and coworkers have also reported a hybrid *O*,*S*-chelating family of aldehydes based on MTM-ethers.[100] Interestingly, as *α*-*O*-substituted aldehydes are the parent substrate, neither the *O*- or *S*-atoms are positioned *β* to the carbonyl. This family of aldehydes were only reported for alkyne hydroacylation reactions (equation 59; **Scheme 24**).

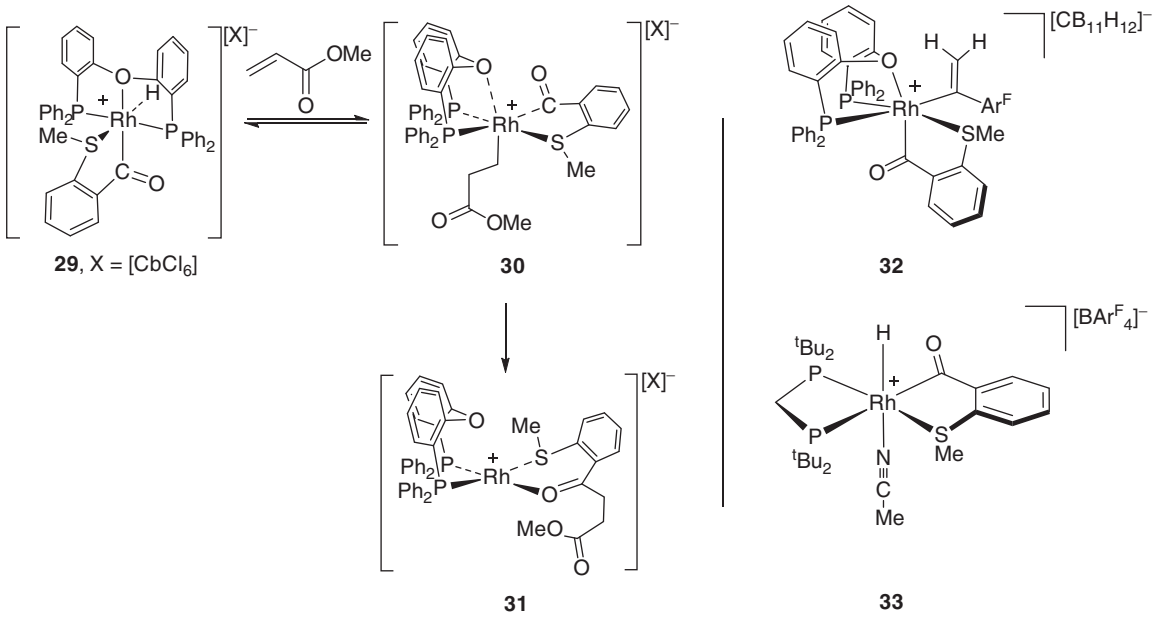
Weller and coworkers have used a variety of *S*-chelating aldehydes to explore the mechanisms in operation with a number of different rhodium-catalyst systems.[101] The use of catalysts incorporating the DPEphos ligand allowed X-ray structure determination of several complexes establishing the formation of the proposed chelated intermediates; for example, a structure of complex **29**, featuring *o*-MeS-benzaldehyde, was solved (**Scheme 25**). In a series of stoichiometric experiments, they also employed NMR and ESI MS/MS techniques to characterize several intermediates further along the catalytic cycle. For example, both complexes **30** and **31**, resulting from the addition of acyl rhodium hydride **29** to methyl acrylate, and then the reductive elimination of the hydroacylation product, respectively, were characterized using these techniques. An important conclusion from their mechanistic studies was that catalysts incorporating the ligand DPEphos suffered reductive decarbonylation at a significantly slower rate than the corresponding dppe-containing systems. They attribute this stability to the hemilabile nature of the tethering oxygen atom in



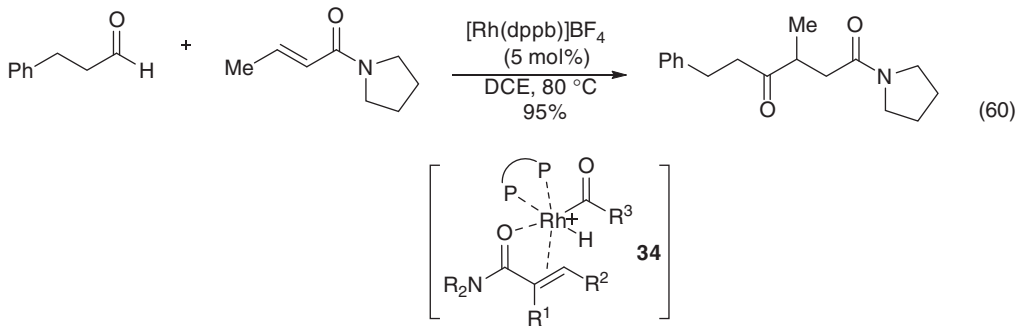
Scheme 24 Applications of rhodium-catalyzed *S*-chelating aldehyde alkyne hydroacylation.

the DPEphos ligand allowing stabilization of the key acyl rhodium intermediates. In the context of alkyne hydroacylation, the use of a DPEphos-derived catalyst allowed the isolation and characterization of a branched alkenyl-rhodium intermediate (**32**);[102] this was the first example of this type of intermediate to be characterized and showed, for the system under study, that hydride migration, and not acyl migration, occurs. For this alkyne hydroacylation/DPEphos system, the authors also showed that hydride migration was irreversible. This observation is in contrast to that made when studying the mechanism of the branched-selective alkyne hydroacylation reactions mediated by bulky *o*-^{i}Pr-dppe-derived rhodium complexes; in these cases, hydride insertion was deemed to be rapid and reversible. Finally, the same group have investigated the mechanism of alkene hydroacylation using rhodium complexes featuring small bite-angle diphosphine ligands.[94] Using these small bite-angle ligands an intermediate acyl rhodium hydride (**33**) was again isolated and characterized, and labeling studies established that both aldehyde oxidative addition and hydride insertion were reversible. The high activity observed with these small bite-angle systems was attributed to a rapid reductive elimination of the final hydroacylation adduct. The variations in mechanism that are observed when changing the exact system under study, in particular substrate type and catalyst, is in line with the reports from Dong and coworkers using *O*-chelating aldehydes.[88]

The vast majority of the rhodium-catalyzed examples discussed so far have featured aldehydes capable of providing stabilization of the key acyl rhodium hydride intermediates by internal coordination, that is, chelation. Tanaka et al. adopted an alternative, but related strategy, based on the use of bidentate binding of the alkene substrates.[103] Using *N*,*N*-dialkylacrylamides as the alkene components they were able to achieve effective intermolecular hydroacylation reactions with a range of aldehydes, including alkyl and aryl variants. An example transformation is shown in equation 60 (Scheme 26), along with the proposed stabilized acyl rhodium hydride species (**34**). A cationic rhodium-bidentate phosphine complex was again employed as the catalyst, although the most effective system was shown to incorporate the dppb ligand, as opposed to the more commonly employed dppe. The use of the less strongly binding methyl acrylate as the alkene component was less successful, and even when employed as solvent, delivered only a 55% yield of the adduct.



Scheme 25 Mechanistic studies using *S*-chelating aldehydes.

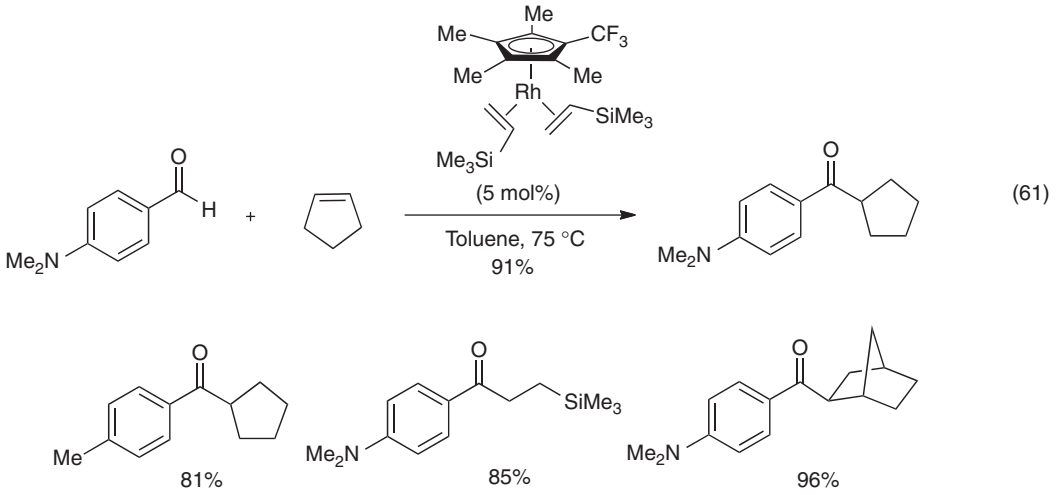


Scheme 26 *N,N*-Dialkylacrylamides as substrates in alkene hydroacylation reactions.

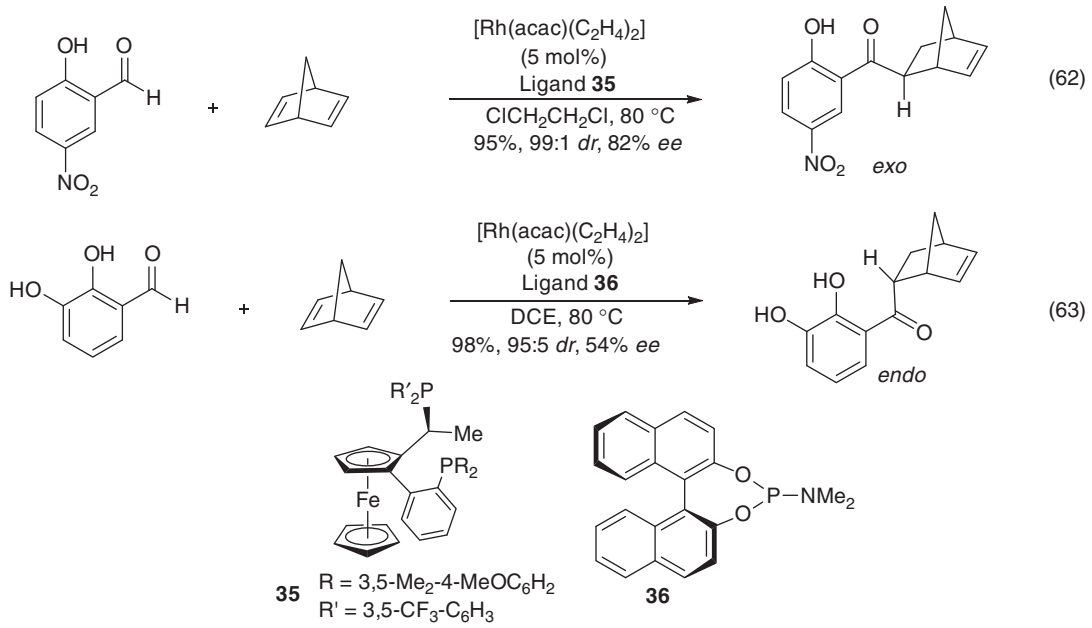
Brookhart and coworkers have also reported on nonchelation controlled rhodium-based methodology for alkene hydroacylation, employing catalysts based on cyclopentadienyl Rh(I)-*bis* olefin complexes.[104] The optimal catalyst featured a CF_3-substituent on the Cp-ring to facilitate faster reductive elimination, and also deliver higher linear selectivity and broader reaction scope. Using this catalyst a variety of aryl aldehydes could be combined with a selection of alkenes in good yields (equation 61). Alkyl aldehydes were not useful substrates under these conditions. Brookhart and coworkers also reported extensive mechanistic investigations using their Rh(I) catalyst system. Kinetic, spectroscopic, and crystallographic methods were used to determine a mechanistic explanation for the observed reactivity. Key observations included the determination of dual catalyst resting-states (the starting bis-olefin complex, and a carbonylated intermediate), that the final reductive-elimination step was the turnover-limiting step of the catalytic cycle, and that all the steps before this were reversible (Scheme 27).

4.17.2.2.1.1 Enantioselective variants

As the development of achiral alkene, alkyne, and allene hydroacylation processes has lagged behind the corresponding intramolecular reactions, it is not surprising that the same trend is true for the enantioselective counterparts. Suemune and Tanaka reported some early work examining diastereoselective reactions,[105] based on the combination of salicylaldehydes with norbornene derivatives; however, Bolm was the first to report an enantioselective intermolecular process, again focusing on additions to norbornene and derivatives.[106] After investigating a wide range of chiral ligands, Bolm and Stemmler were able to catalyze the addition a range of salicyclaldehyde derivatives to norboradienes (Scheme 28). They could achieve an interesting diastereoselectivity switch by choosing to employ either a monodentate or bidentate chiral phosphine ligand. For example, use of the ferrocene-derived diphosphine (**35**) delivered *exo*-adduct with 82% *ee* (equation 62), whereas the use of monodentate phosphoramidate ligand **36** allowed the formation



Scheme 27 Brookhart's rhodium-catalyzed alkene hydroacylation.

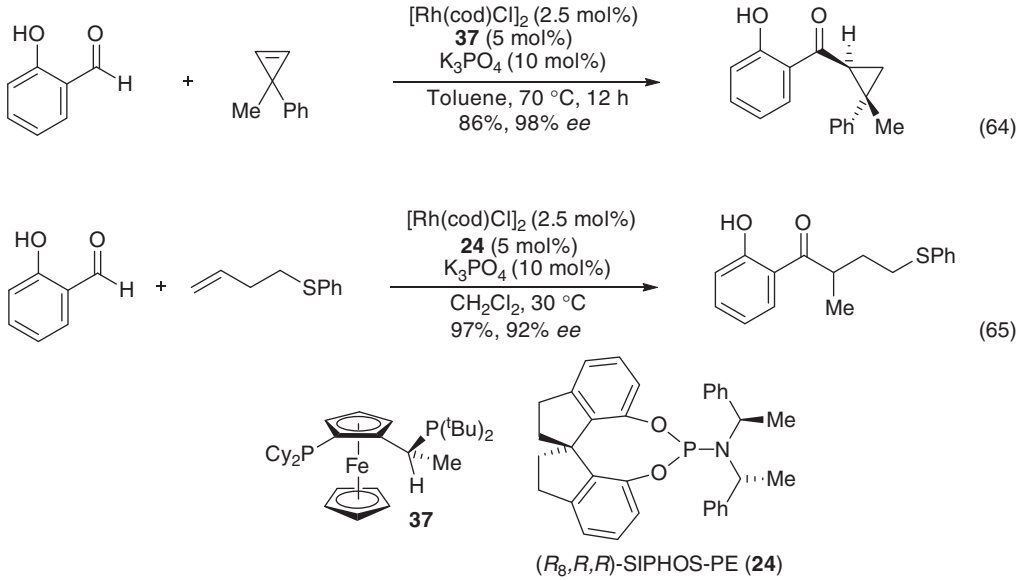


Scheme 28 Bolm's enantioselective norbornadiene hydroacylation.

of *endo*-adduct, this time in 54% *ee* (equation 63). This reversal in selectivity was rationalized by considering mono- or bidentate binding of the norbornadiene, dependent on the binding of the corresponding *P*-ligand.

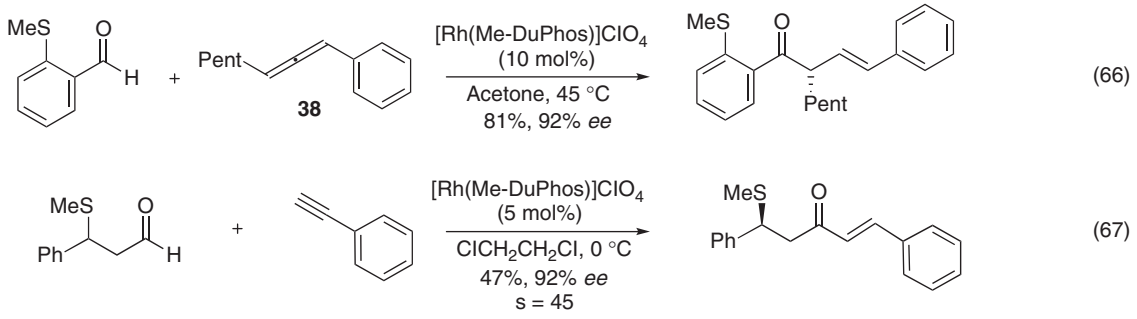
Recently Dong and coworkers have also explored the enantioselective addition of salicylaldehydes to alkenes. One of the reasons that Bolm and Stemmler employed norbornene-derivatives as the alkene components in their enantioselective chemistry is that achieving the required reactivity with substituted alkenes, that is, the alkenes needed to form a stereogenic *C*-atom, is challenging and the high reactivity of these strained bicyclic scaffolds is beneficial. Dong and coworkers utilized a related approach and again employed *O*-chelating salicylaldehydes, but combined them with highly reactive, strained, cyclopropenes.[107] By employing a catalyst incorporating a bidentate ferrocene-derived unit, they were able to hydroacylate disubstituted cyclopropenes to deliver the desymmetrized products in very good yields, with excellent enantioselectivity and generally good diastereoselectivity (equation 64). Good variation of the substitution pattern on the salicylaldehyde and the cyclopropene were achieved. In a second enantioselective process Dong and coworkers utilized chelating-alkenes to achieve branched-selective additions to terminal alkenes. Homoallylic sulfide-substituents proved effective at controlling the regioselectivity, and the use of a phosphoramidate ligand ensured high enantiocontrol (equation 65).[108] As before, good variation of substitution on each coupling partner was possible. The authors were also able to show that a 1,2-disubstituted alkene could be employed efficiently. The Dong chemistry is

an effective demonstration of related work from Suemune and Tanaka, who employed 1,5-hexadiene substrates to achieve modest levels of branched selectivity, but were only able to achieve moderate enantioselectivities (see **Scheme 19** for the achiral versions of these reactions) (**Scheme 29**).[109]



Scheme 29 Enantioselective hydroacylation using cyclopropenes and homoallylic sulfides. Absolute stereochemistry not provided for equation 65.

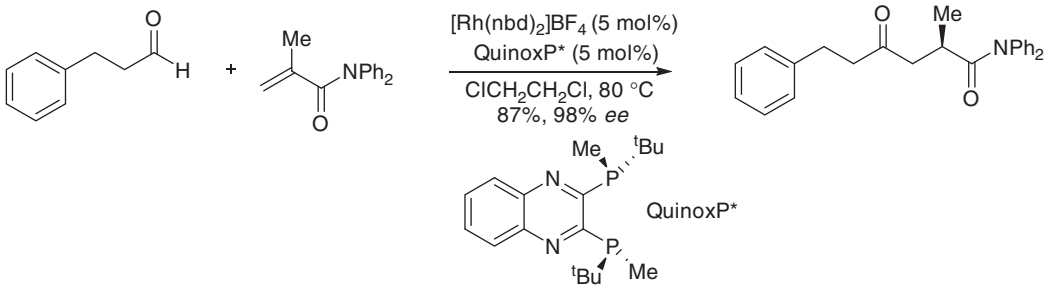
Willis and coworkers have reported an enantioselective variant of their intermolecular hydroacylation system employing *β-S*-substituted aldehydes. To obtain sufficient reactivity in the alkene components the authors employed 1,3-disubstituted allenes as substrates (for an earlier example of allene hydroacylation see equation 52). For example, reaction between pentyl, phenyl-disubstituted allene **38** and aromatic *o*-MeS-benzaldehyde, employing a Me-DuPhos-derived cationic rhodium catalyst, delivered the corresponding *β,γ*-enone in 81% yield and 92% *ee* (equation 66); good variation of the allene substituents was possible. Willis and coworkers found that it was necessary to employ an aromatic aldehyde to maintain high enantioselectivity. The authors also established that the process proceeded by way of a dynamic kinetic asymmetric transformation, involving racemization of the allene during the course of the reaction.[110] Willis and coworkers have also reported the catalytic enantioselective kinetic resolution of racemic *β-S*-substituted aldehydes using Rh-catalyzed alkyne hydroacylation.[111] Selection of an appropriate chiral diphosphine ligand allowed the selective kinetic resolution of *β-S*-chelating aldehydes bearing a stereocenter at either the *α*- or *β*-position. Selectivity factors (s) for the isolated products were in the range $s = 12–45$ for *β*-substituents, and $s = 9–34$ for the *α* examples. Equation 67 gives an example of a *β*-aryl-substituted aldehyde, for which DuPhos-derived catalysts were found to be optimal (**Scheme 30**).



Scheme 30 Enantioselective catalysis using *β-S*-chelating aldehydes.

Tanaka and Shibata have extended their acrylamide-based hydroacylation chemistry to include an enantioselective variant. Using the same type of strongly binding *N,N*-disubstituted acrylamides in combination with a QuinoxP*-derived cationic rhodium catalyst, the group was able to employ a variety of alkyl aldehydes to deliver the adducts with excellent enantioselectivities (equation 68).[112] The use of both an *α*-methyl and an *α*-phenyl substituent was possible on the acrylamide, however, aryl aldehydes were poor substrates. One example of an arylamide bearing a tri-substituted alkene was also employed, allowing the

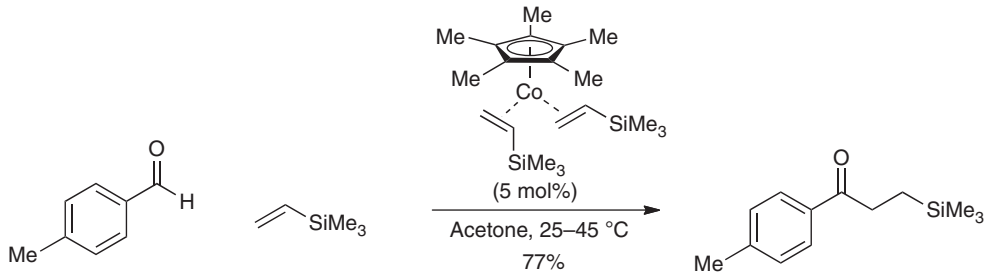
formation of an adduct featuring two stereogenic centers; unfortunately, although excellent enantio- and diastereo-control were achieved, only very low reactivity was observed.



(68)

4.17.2.2.2 Cobalt catalysis

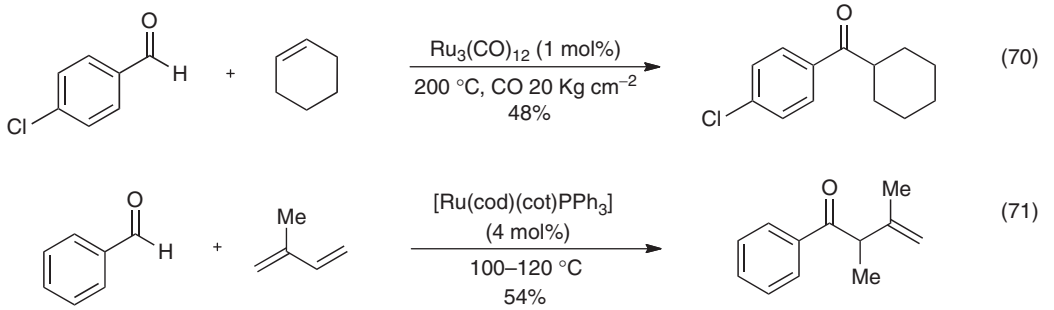
Brookhart and coworkers have described a cobalt-based hydroacylation method related to their rhodium-catalyzed chemistry (see Scheme 27). The cobalt system again employed a Cp-derived catalyst, and was effective for the combination of a good range of aromatic and alkyl aldehydes with vinylsilanes (equation 69).[113,114] Although low to moderate temperatures, as well as low-catalyst loadings (as low as 0.5 mol%) could be employed, the reaction was limited by the need to use vinylsilanes as the only class of alkene substrate. As might be expected, reductive decarbonylation is again a problematic side-reaction for cobalt-based hydroacylation methods.



(69)

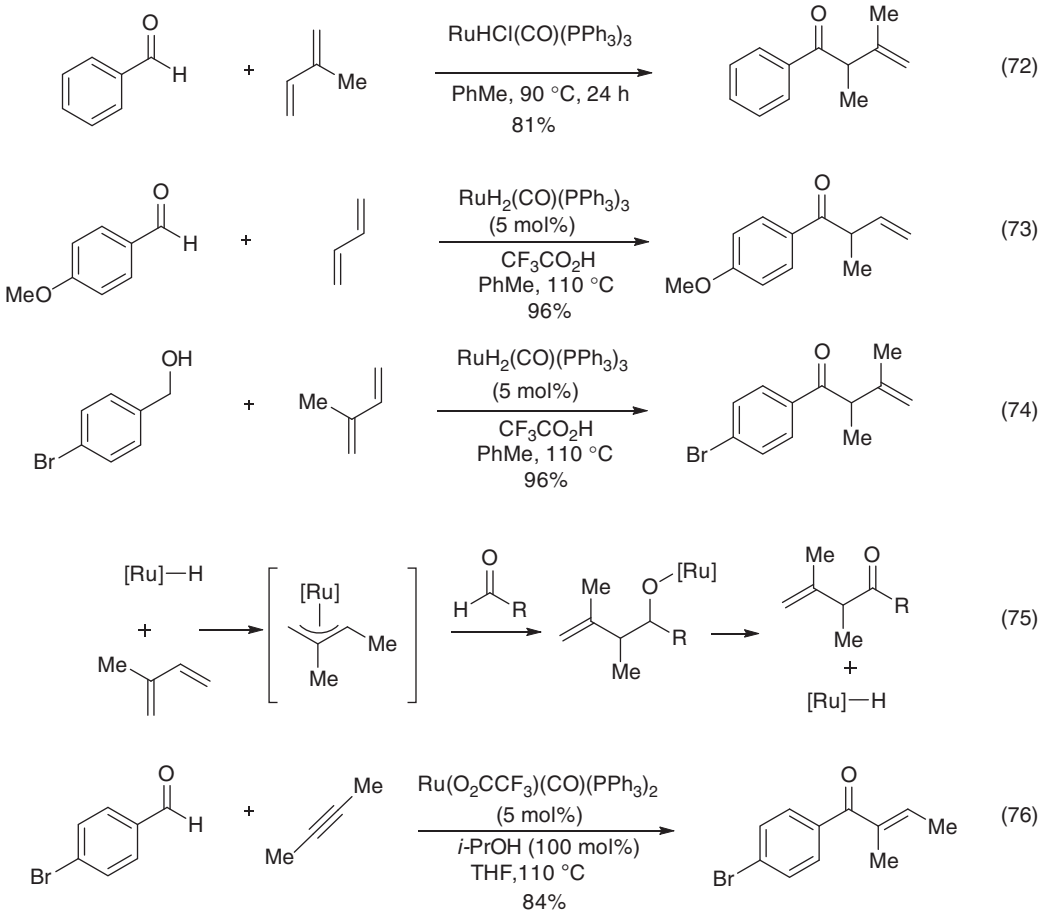
4.17.2.2.3 Ruthenium catalysis

Early reports of Ru-catalyzed intermolecular hydroacylation reactions described only low yielding processes that that were plagued by the formation of Cannizzaro and Tishchenko-type side products.[115] Despite subsequent reports of Ru-catalysts effecting related alkyl formate-alkene coupling reactions appearing,[116,117] it was not until 1987 that a more successful Ru-catalyzed hydroacylation method was described. Watanabe and Kondo were able to show that aryl and hetero-aryl aldehydes could be combined with a range of alkenes using $Ru_3(CO)_{12}$ as the catalyst (equation 70).[118,119] By employing a relatively high CO pressure of 20 Kg cm^{-2} (284 psi) and a temperature of 200 °C, it was possible to use catalyst loadings of only 1 mol%. Simple acyclic and cyclic alkenes could be combined with aromatic aldehydes in moderate yields. Aliphatic aldehydes could not be employed and instead led to the formation of transformylation products. The same group subsequently explored the Ru-catalyzed hydroacylation of 1,3-dienes.[120] By employing [Ru(cod)(cot)PPh_3] as the catalyst, the group was able to show that the addition of aromatic aldehydes to 1,3-dienes was possible (equation 71). A CO atmosphere was not employed although the dienes were employed as solvent. The authors proposed that the key intermediates were (acyl)(η^3-allyl)ruthenium complexes (Scheme 31).



Scheme 31 Early examples of ruthenium-catalyzed hydroacylation reactions.

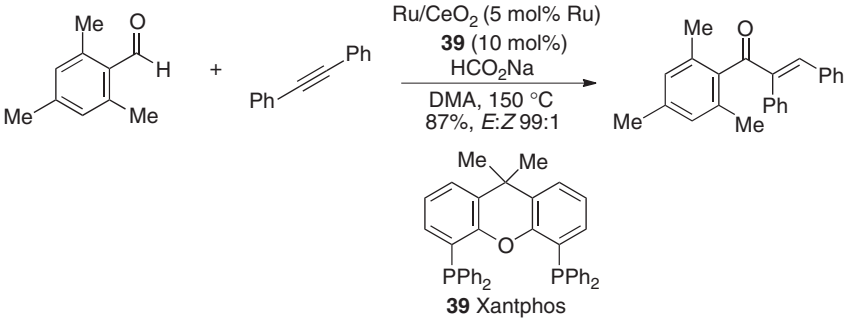
In 2008, both Ryu and coworkers and Krische and coworkers reported the hydroacylative ruthenium-catalyzed addition of 1,3-dienes to aldehydes (Scheme 32). Ryu and coworkers found the ruthenium hydride catalyst, $RuHCl(CO)(PPh_3)_3$, used at 90 °C in toluene, promoted the coupling between a variety of 1,3-dienes and aryl and alkyl aldehydes (equation 72).[121] Branched β,γ-unsaturated ketones were obtained as the products in good to excellent yields. Building from their earlier work on Ru-catalyzed homoallylic alcohol synthesis, Krische and coworkers employed ruthenium-catalyzed transfer hydrogenation conditions to effect efficient coupling between 1,3-dienes and either aldehydes or alcohols, to generate hydroacylation adducts (equations 73 and 74).[122] They utilized the complex $RuH_2(CO)(PPh_3)_3$, in combination with trifluoroacetic acid, to generate the required ruthenium hydride, which could be used to couple a wide range of substituted dienes with both aryl and alkyl aldehydes in excellent yields. Identical reaction conditions were used for both the aldehyde and alcohol coupling reactions. The branched-selective products, obtained from using both the Ryu and Krische chemistries, are notable, and differ from the more usual linear-selective processes delivered by the majority of alternative intermolecular hydroacylation reactions. These ruthenium hydride-mediated processes are mechanistically distinct from the earlier Ru and Rh examples, and importantly, avoid the formation of acyl-metal intermediates. Both the Krische and Ryu proposed similar mechanisms, which involves initial formation of π-allylruthenium intermediates, which then undergo addition to the relevant aldehyde to generate alkoxide intermediates, which can undergo β-hydride elimination to generate the formal hydroacylation products (equation 75). Krische and coworkers have also applied their ruthenium-catalyzed transfer hydrogenation-based chemistry to alkyne hydroacylation (equation 76).[123] By using $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as the catalyst, in the presence of an equivalent of isopropanol, aryl aldehydes and 2-butyne could be combined in good yields. A nonsymmetrical alkyne could also be coupled in good yield, but provided a mixture of regioisomers. Again, the group was also able to obtain hydroacylation adducts from the combination of appropriate benzylic alcohols and 2-butyne. The only difference in reaction conditions, relative to the aldehyde process, was the removal of isopropanol.



Scheme 32 Ruthenium-catalyzed diene and alkyne hydroacylation.

In 2012, Wada and Inoue reported the ceria-supported ruthenium-catalyzed hydroacylation of internal alkynes.[124] The authors used a catalyst system generated from CeO_2-supported Ru (Ru/CeO_2), in combination with HCO_2Na and the phosphine ligand Xantphos. Using this combination, a broad range of aryl and hetero-aryl aldehydes were combined with a number of internal alkynes, delivering the expected enone products in moderate to good yields (equation 77). Varied *E*:*Z* selectivity was generally obtained; however, if sterically demanding di-*o*-substituted aldehydes were used then enone products were obtained with high

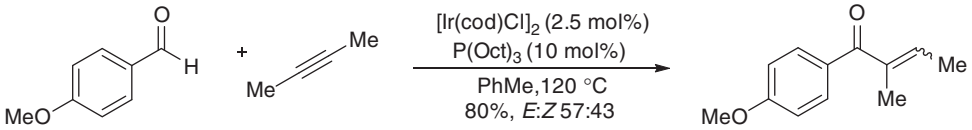
E-selectivity. Catalyst recycling was demonstrated, although reactivation, involving calcination at 400 °C was involved. Although detailed mechanistic studies were not reported, the authors propose a catalytic cycle which involves the initial formation of a Ru (0) center which undergoes oxidative addition with an aldehyde to generate an acyl-metal hydride intermediate. They speculate that significant decarbonylation was not seen because of the use of sterically demanding *o*-substituted aldehydes.



(77)

4.17.2.2.4 Iridium catalysis

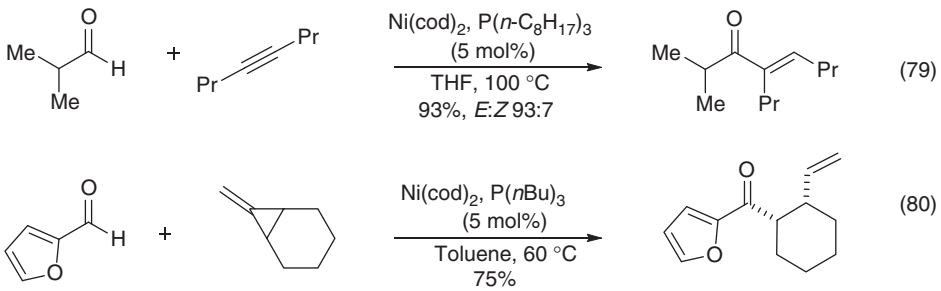
Obora and Ishii have exploited Ir-based transfer hydrogenation catalysts to achieve intermolecular alkyne hydroacylation reactions.[125] In work very much related to the Krische and Ryu chemistry (see Scheme 30), Obora, Ishii and coworkers were also able to combine both alcohols and aldehydes with 2-alkynes to deliver hydroacylation adducts. The effective catalyst was generated from $[Ir(cod)]_2$ and $P(Oct)_3$, and when used in toluene at 120 °C, delivered good yields of the desired adducts, although with poor *E*:*Z* selectivity (equation 78). A number of aryl aldehydes were effectively used, although 2-butyne was the only alkyne employed. Mechanistically, the reactions were proposed to proceed via hydrometallation and isomerization, to generate a hydrido(π-allyl) iridium intermediate. Combination with the relevant aldehyde then forms an initial homoallylic alcohol, which is then oxidized to the corresponding ketone, and a final double-bond isomerization delivers the conjugated enone products.



(78)

4.17.2.2.5 Nickel catalysis

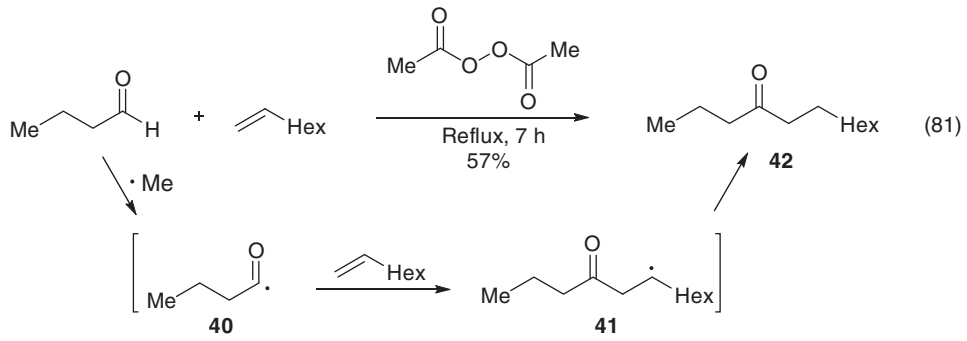
Although there are no examples of simple nickel-catalyzed alkene hydroacylation reactions, the corresponding alkyne chemistry has been reported. Tsuda demonstrated that Ni(0) complexes could be used to combine simple aryl and alkyl aldehydes with symmetrical internal alkynes (equation 79).[126] The use of *n*-alkyl phosphines as ligands allowed formation of the enone products with high *E*-selectivity. Aryl or bulky alkyl phosphines generated mixtures of enone and dienone products. Unsymmetrical alkynes led to regioisomeric product mixtures. Although no detailed mechanistic studies were undertaken the authors propose two mechanistic scenarios; one involving an acyl nickel hydride intermediate, and a second involving a Ni(II) metallacycle as the key intermediate. Recent work from Nakao has focused on the related nickel-catalyzed hydrocarbamoylation of alkynes. Suginome and coworkers have reported the nickel-catalyzed ring-opening hydroacylation of methylenecyclopropanes to deliver γ,δ-unsaturated ketone products.[127] Using reaction conditions closely related to the Tsuda system, they were able to combine a variety of aromatic aldehydes and a single alkyl aldehyde with a range of methylenecyclopropanes (equation 80). Suginome and coworkers proposed a mechanism which proceeds through an acyl nickel hydride intermediate (Scheme 33).



Scheme 33 Intermolecular nickel-catalyzed hydroacylation chemistry.

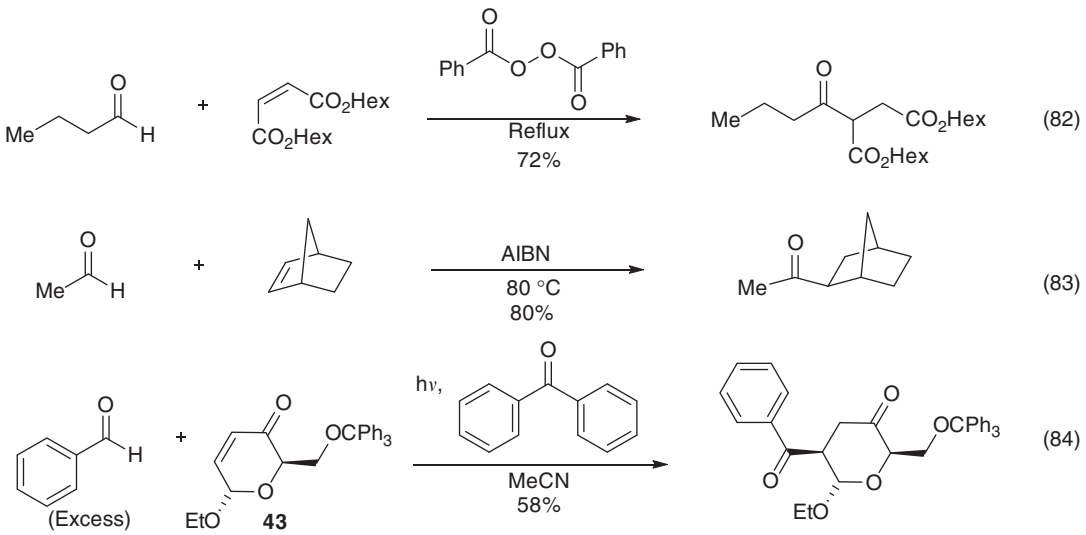
4.17.3 Radical Methods

Radical-mediated alkene hydroacylation methods predate the earliest metal-catalyzed examples, with Kharasch reporting the diacetyl peroxide initiated, as well as the photochemically initiated, addition of alkyl aldehydes to terminal alkenes.[128] The overall process is shown in equation 81 (Scheme 34), and involves abstraction of a formyl hydrogen atom to generate an acyl radical (**40**), followed by addition to the alkene to form secondary alkyl radical **41**. Finally, abstraction of a formyl hydrogen atom by alkyl radical **41** leads to the ketone product (**42**) and regenerates an acyl radical to continue the chain process.[129] The moderate yield of the desired ketone was attributed to the formation of polymeric material resulting from addition of alkyl radical **41** to further alkene. This stems from the abstraction of the formyl hydrogen atom being a relatively slow process, as alkyl radical **41** is nucleophilic in character. The reactions could also be initiated photochemically; in these cases, aldol side products were often formed as a result of the acid generated during the reactions.



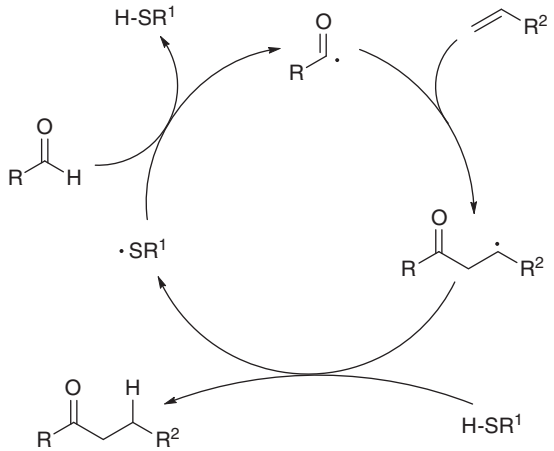
Scheme 34 Kharasch's initial radical alkene hydroacylation reaction.

Patrick followed up the Kharasch chemistry with reports detailing the benzoyl peroxide initiated addition of aldehydes to maleates (equation 82).[130,131] By using an excess of aldehyde (2–3 equivalents) good yields of the target ketones were achieved. For example, the addition of butanal to dihexyl maleate delivered the corresponding ketone in 72% yield. Fumerates were less useful, delivering lower yields and greater amounts of polymeric side products. Related additions to enones, enoates, and to perfluoroalkenes,[132] have also been reported. Neckers has exploited the higher reactivity of electron-poor alkenes in these radical-mediated hydroacylation reactions in the development of simple cascade processes.[133] The use of strained alkenes was needed to achieve reactivity with nonelectron-poor systems. For example, Stockman reported the addition of acetaldehyde to norbornene using azobisisobutyronitrile (AIBN) as an initiator (equation 83); the *exo*-adduct was isolated in a respectable 80% yield.[134] In an alternative approach, Fraser-Reid employed a large excess of the aldehyde component in the addition to carbohydrate-derived enones, using photochemical initiation.[135] For example, benzaldehyde was combined with enone **43** in 58% yield (equation 84; Scheme 35).



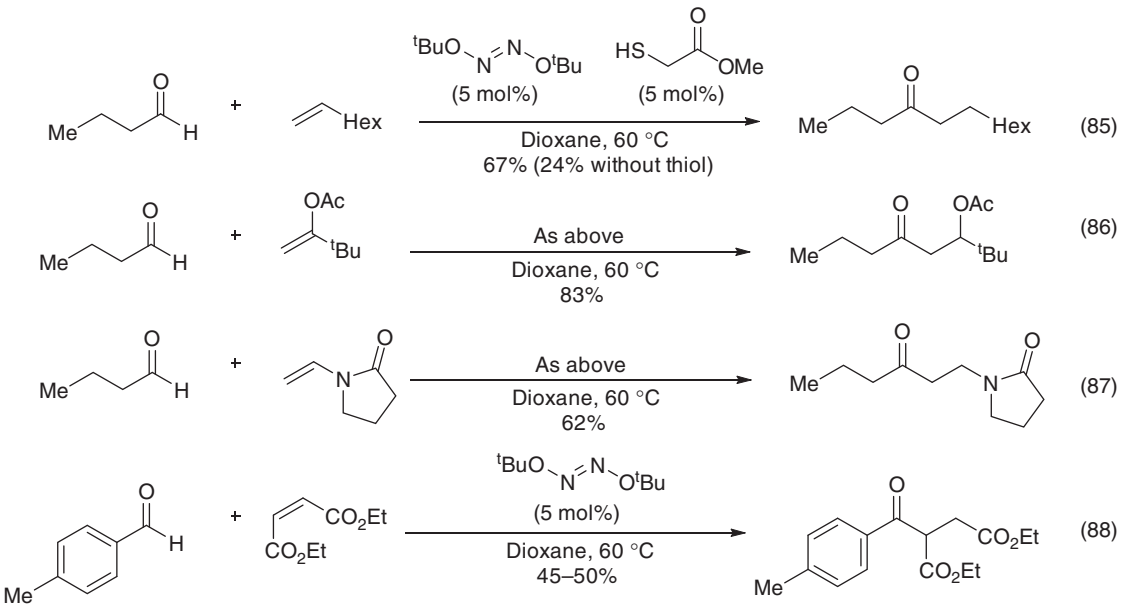
Scheme 35 Radical addition to maleates, norbornene, and a glucal.

Roberts has applied the concept of 'polarity reversal catalysis' to radical-mediated alkene hydroacylation and in doing so has established one of the most general radical-based methods for these types of reaction.[136,137] The approach relies on the use of a thiol catalyst to accelerate the inefficient formyl hydrogen abstraction step (**41**→**42**, Scheme 33), and is effective as the intermediate thiyl radical that is generated is electrophilic in character, and is thus more effective for this process than the corresponding nucleophilic alkyl radical. The overall process is illustrated in Scheme 36.



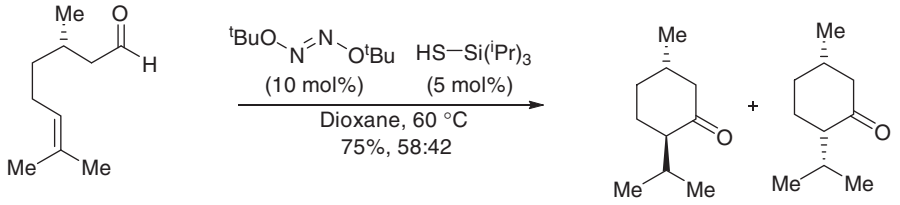
Scheme 36 Polarity reversal catalysis applied to alkene hydroacylation.

The realization of the general process shown in Scheme 36 involved the use of *tert*-butyl hyponitrite as the radical initiator and methyl thioglycolate as the thiol catalyst.[136] The reaction between butanal and octene illustrates the effect of the thiol catalyst; a reaction employing the thiol allowed the ketone product to be obtained in 67% yield, whereas in the absence of thiol the same ketone was isolated in 24% (equation 85). The effect of the thiol is particularly apparent with electron-neutral and electron-rich alkenes, and less so with electron-poor alkenes, presumably as the alkyl radicals formed from addition to the electron-poor alkenes are themselves more electrophilic, and therefore more competent in formyl hydrogen abstraction. The reactions were generally performed in dioxane at 60 °C, and allowed the addition of aldehydes to neutral (equation 85), electron-rich (equations 86 and 87), and electron-poor alkenes (equation 88). As can be seen, the method is tolerant of a variety of functional groups (Scheme 37).



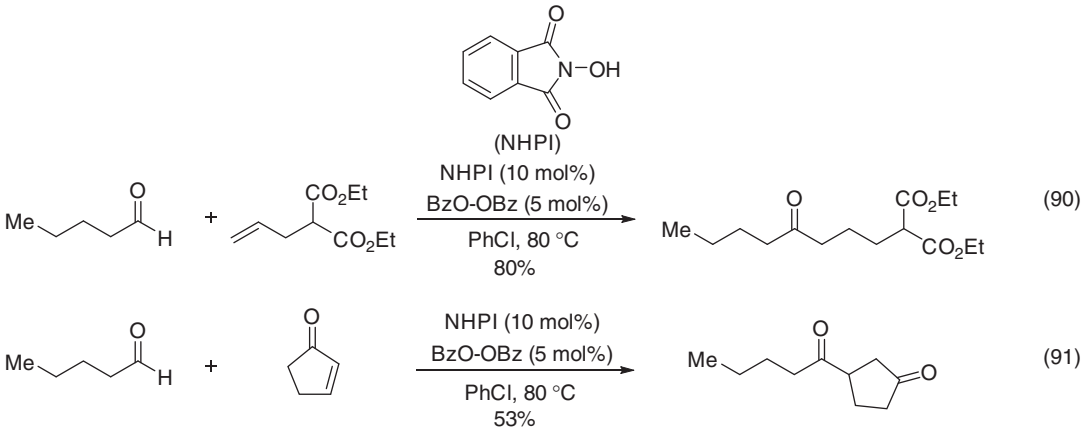
Scheme 37 Examples of polarity reversal catalysis applied to intermolecular alkene hydroacylation.

Roberts subsequently went on to demonstrate that the same polarity reversal catalysis could be applied to intramolecular alkene hydroacylation.[137] For example, cyclization of citronellal was achieved by treatment with *tert*-butyl hyponitrite as initiator, and triisopropylsilyl thiol as catalyst, to deliver the diastereomeric cyclohexanone products in 75% yield (equation 89). This represented a significant improvement on earlier reports of peroxide-mediated reactions.



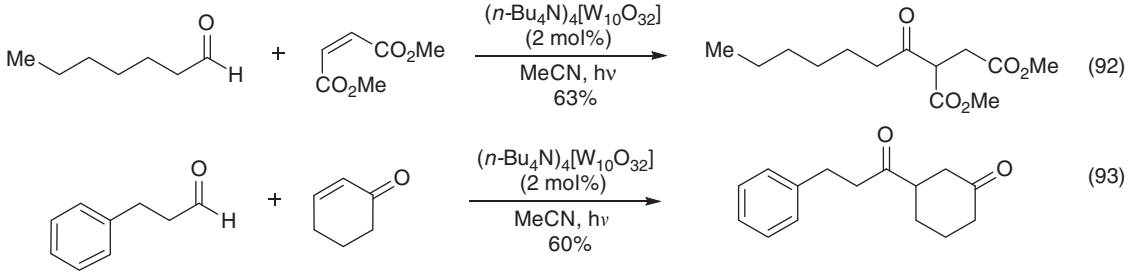
(89)

Ishii and coworkers have expanded the Roberts chemistry to include a different class of polarity reversal catalysts. In the Ishii chemistry, *N*-hydroxyphthalimide (NHPI) is used as the catalyst, in combination with dibenzolyl peroxide as the initiator in toluene at 80 °C.[138,139] Using this system, propanal, pentanal, and benzaldehyde were combined with simple alkenes in good yields (equation 90). Provided a strained system, or an electron-withdrawing group was employed, internal alkenes could also be used successfully (equation 91; **Scheme 38**).



Scheme 38 Polarity reversal catalysis using NHPI.

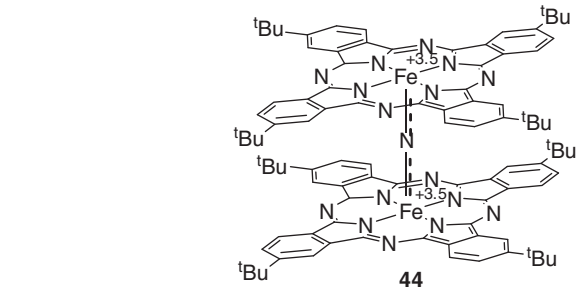
Fagnoni and coworkers have exploited tetrabutylammonium decatungstate (TBADT), activated photochemically, to catalyze intermolecular alkene hydroacylation reactions.[140] Photochemically activated decatungstate abstracts the initial formyl hydrogen atom and also serves to transfer the hydrogen atom to the subsequently formed alkyl radical. In the optimized system the authors were able to employ equimolar amounts of aldehyde and alkene and to employ only 2 mol% of the TBADT catalyst (equations 92 and 93). The chemistry proved to be efficient provided that electron-poor alkenes were employed (**Scheme 39**). Fagnoni and coworkers went on to show that solar light was also effective at promoting these transformations.[141]



Scheme 39 Decatungstate-photocatalyzed hydroacylation.

Sorokin and coworkers have developed the use of iron phthalocyanine complexes as catalysts for alkene hydroacylation.[142] The method employs the iron phthalocyanine complex as a catalyst in combination with *tert*-butyl hydroperoxide as initiator. The iron complex initially decomposes the *tert*-butyl hydroperoxide to generate a *tert*-butoxide radical, which then abstracts the formyl hydrogen atom. The acyl radical thus generated adds across the alkene to form an alkyl radical. A reduced form of the catalyst then

delivers a hydrogen atom to the initially formed alkyl radical, thus generating the hydroacylation adduct and forming an oxo-variant of the catalyst, which is capable of formyl hydrogen abstraction, thus allowing completion of the catalytic cycle. The optimized process requires a 10-fold excess of aldehyde to avoid side-product formation, and is performed neat at 60 °C. Complex **44** was used at the low loading of only 0.01 mol%, and 15 mol% ^{t}BuOOH was needed as initiator. Using these conditions, acetaldehyde was effectively combined with internal and terminal alkenes to deliver the hydroacylation adducts in good yields (equations 94 and 95). The selectivity indicated in Scheme 40 refers to the hydroacylation product relative to all other products, the majority of which arise from allylic oxidation of the alkene, and dimerization of the alkene. No other aldehyde substrates were demonstrated.



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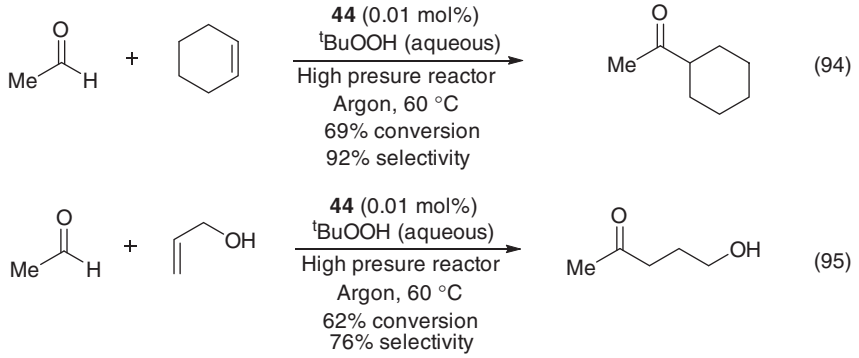


Scheme 40 Iron phthalocyanine-catalyzed alkene hydroacylation.

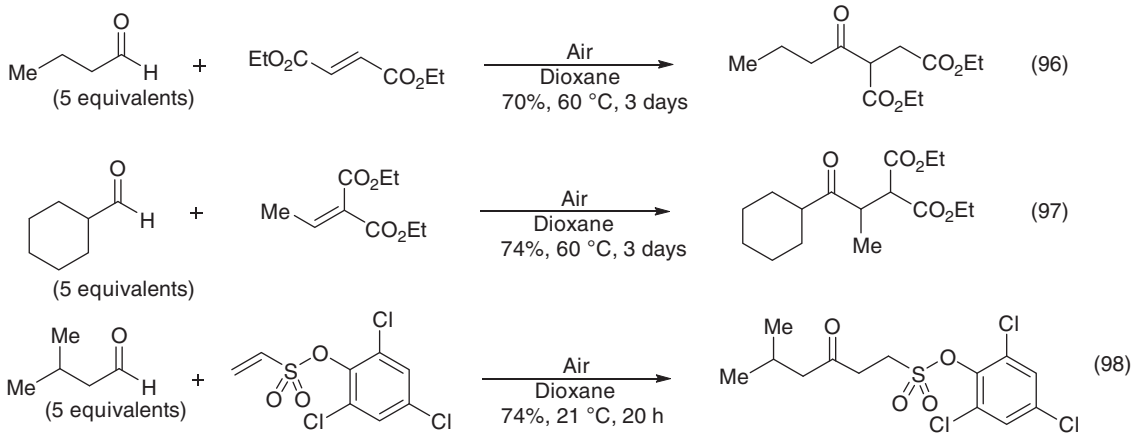
As can be seen from the preceding schemes in this Section 4.17.3, a variety of catalysts and initiators have been used to promote radical-based alkene hydroacylation reactions. All are effective for certain substrate combinations, but the need to use a catalyst and/or an initiator diminishes the inherent atom-economic nature of hydroacylation reactions. Caddick and coworkers have reported an approach to radical-based hydroacylation chemistry that attempts to rectify these shortcomings.[143–146] Caddick and coworkers made the observation that acyl radicals are intermediates in the oxygen-promoted auto-oxidation of aldehydes to carboxylic acids. They reasoned that under appropriate conditions it should be possible to trap the acyl radicals with alkenes and thus deliver hydroacylation products. The major advantage of this method is that only molecular oxygen would be required as a reagent. Caddick and coworkers were able to validate their proposal and found that a range of alkyl aldehydes could be combined with electron-poor alkenes in good yields (Scheme 41). As exposure to molecular oxygen is a requirement of the process, the authors found that careful control of concentration and temperature was needed to achieve efficient reactions. Although the requirement for electron-poor alkenes is a limitation, the process was tolerant of a broad range of functional groups, and a variety of electron-withdrawing substituents, including esters, sulfonate esters, and phosphonates could be used (equations 96–98).

Preliminary mechanistic studies from the Caddick group, including the dependence on molecular oxygen, the inhibition of the reaction with the addition of BHT, and the formation of radical-derived side products, supported the proposed radical mechanism, which is summarized in Scheme 42.[145] The cycle closely resembles the earlier scheme, but with the exclusion of a specific initiator; instead, this role is performed by molecular oxygen, leading to the formation of the key initial acyl radical.

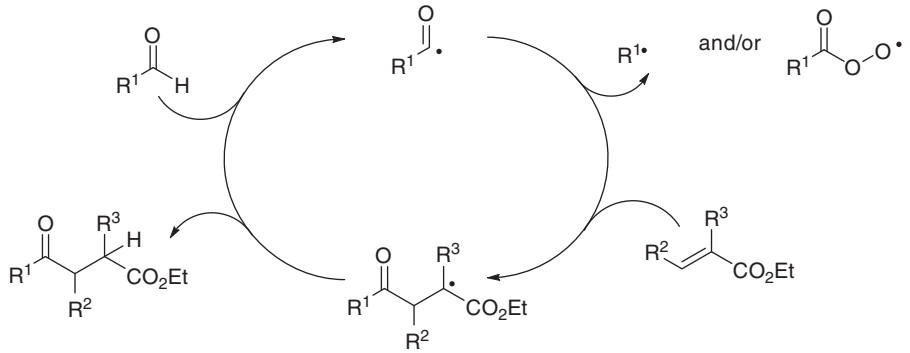
4.17.4 Organocatalytic Methods

4.17.4.1 Intramolecular Reactions

A formal organocatalytic hydroacylation reaction, the Stetter reaction, has been known since 1974,[147] and in its original form – the conjugate addition of an aldehyde umpolung to a Michael acceptor – is the subject of a vast literature. Consideration of the classic



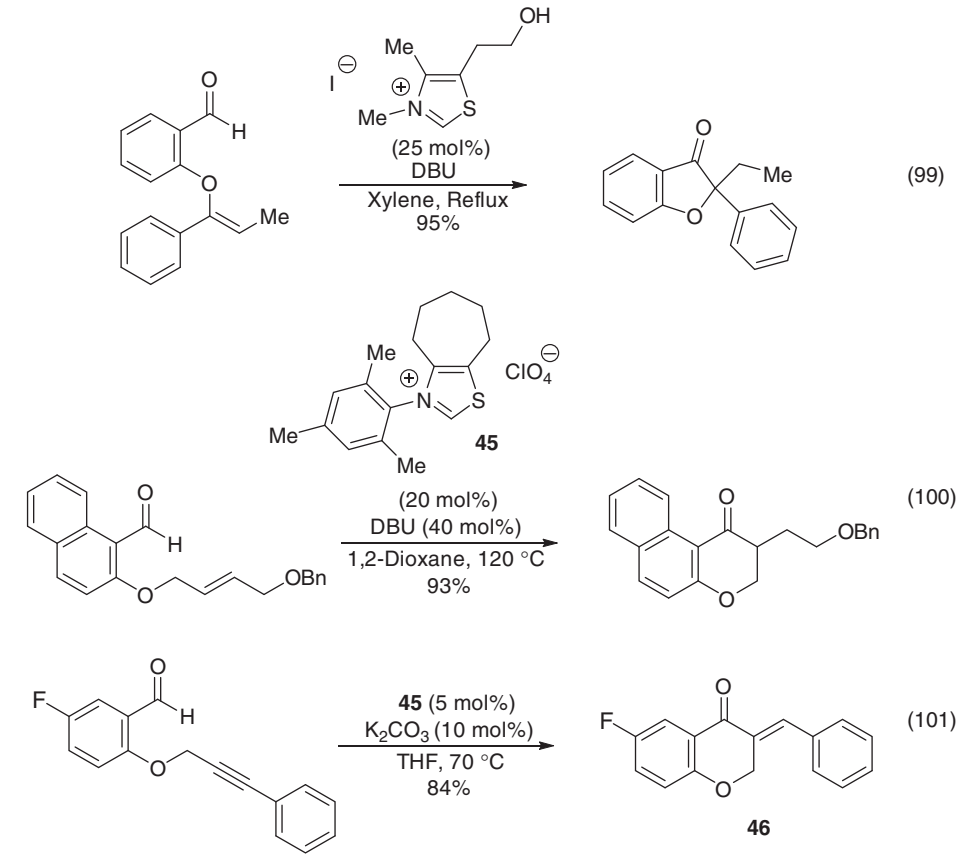
Scheme 41 Molecular oxygen-promoted alkene hydroacylation.



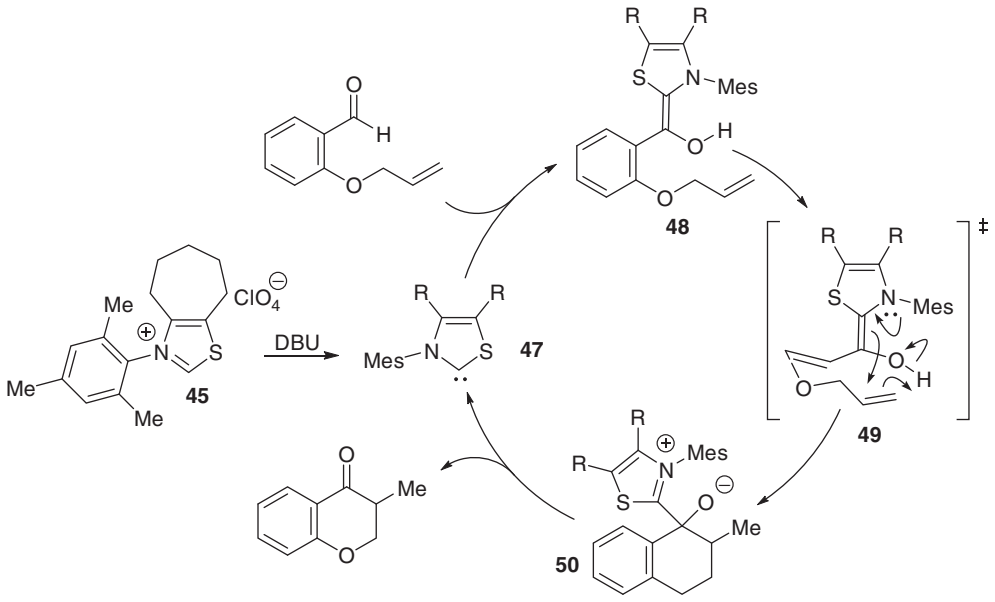
Scheme 42 Proposed mechanism for oxygen-promoted alkene hydroacylation.

Stetter reaction is beyond the scope this chapter, and is later dealt with in detail (*see* Chapter 4.23). However, recently, examples of related reactions in which aldehyde umpolungs, generated using NHCs, are combined with alkenes not conjugated to anion stabilizing groups have begun to be reported. These processes, which formally combine aldehydes with nonpolar alkenes are hydroacylation reactions and have been achieved in both intra- and intermolecular variants. In the classic Stetter process an NHC is combined with an aldehyde to generate a weakly nucleophilic 'Breslow intermediate' which then adds to an electron-poor alkene. The first examples of Breslow intermediates combining with alternative types of alkenes, the so-called 'unconventional reaction partners,' can be found in the work of She in the context of a benzofuranone synthesis (equation 99; **Scheme 43**).[148] She and coworkers found that treatment of aldehydes tethered to an enol ether, when combined with a thiazolium salt and base, delivered the corresponding benzofuranone. This concept was then expanded on by Glorius and coworkers, who produced an efficient synthesis of chromanones from the cyclization of 2-allyloxy benzaldehydes using NHC catalysts.[149] After evaluating a range of potential catalysts, mesityl-substituted thiazolium salt **45** was found to be most effective, and promoted the desired transformation with good efficiency (equation 100). A relatively high catalyst loading of 20 mol% was employed, and the active carbene was generated by treatment with 1,8-diazabicycloundec-7-ene (DBU). Variation of the substituents on both the arene and the allyl unit of the substrates was possible. The same thiazolium salt, this time in combination with K_2CO_3 was also shown to promote similar cyclizations onto electron-neutral alkynes (equation 101).[150] The greater reactivity of alkynes in these cyclization processes allowed catalyst loadings of 5 mol% to be employed. Again, good variation of the substitition pattern on the substrates was possible. The same group went on to show that the products of alkyne cyclization, that is, chromanone **46**, featuring an *exo*-alkene could be combined with a second aldehyde in a classic Stetter-type process.

A proposed mechanism for the NHC-catalyzed intramolecular alkene hydroacylation process is shown in **Scheme 44**.[151,152] Addition of the NHC (**47**) to the aldehyde carbonyl generates Breslow intermediate **48**. This intermediate is then proposed to proceed via a concerted but asynchronous transition state **49** to generate zwitterionic intermediate **50**. Transition state **49** captures the 'dual activation' possible using NHC catalysts; the positively polarized proton of **49** activates the alkene, whereas the nucleophilic enamine starts to attack the now activated coupling partner. The mechanism is completed by the collapse of zwitterion **50** to generate the chromanone product and release the NHC catalyst. Density functional theory calculations support the proposed mechanism.[153]

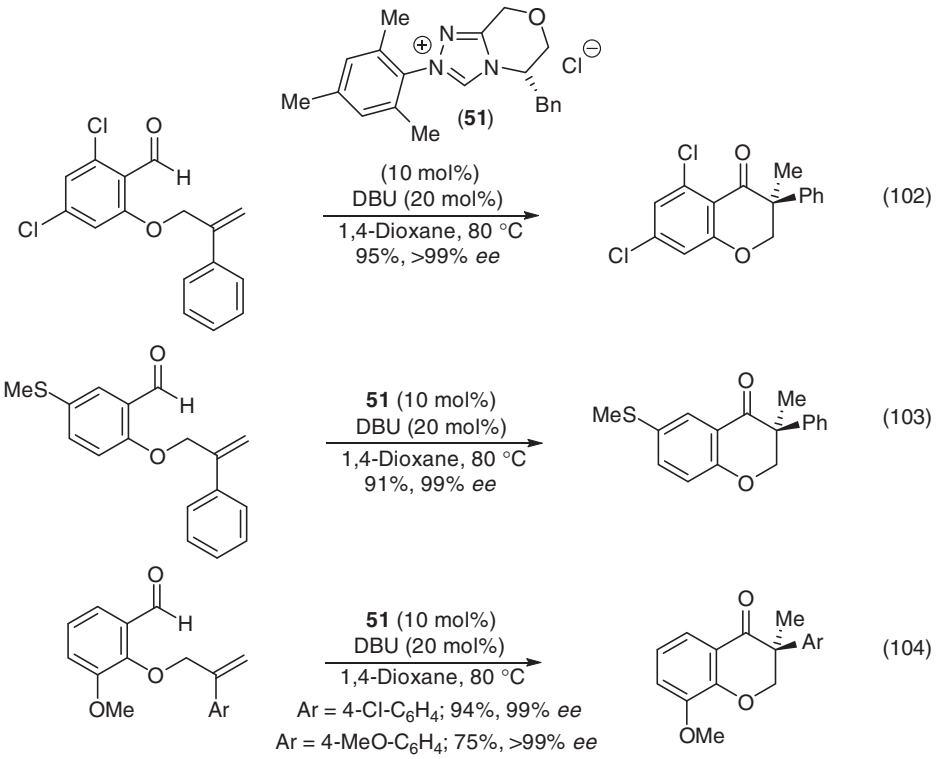


Scheme 43 NHC-catalyzed intermolecular hydroacylation reactions.



Scheme 44 The mechanism of NHC-catalyzed intramolecular alkene hydroacylation.

Glorius and coworkers have gone on to develop an asymmetric variant of their intramolecular alkene hydroacylation chemistry using an enantiomerically enriched NHC catalyst.[153] The carbene generated from triazolium salt **51** using DBU, was shown to promote the desired cyclizations to deliver chromanones featuring all-carbon quaternary centers (Scheme 45).



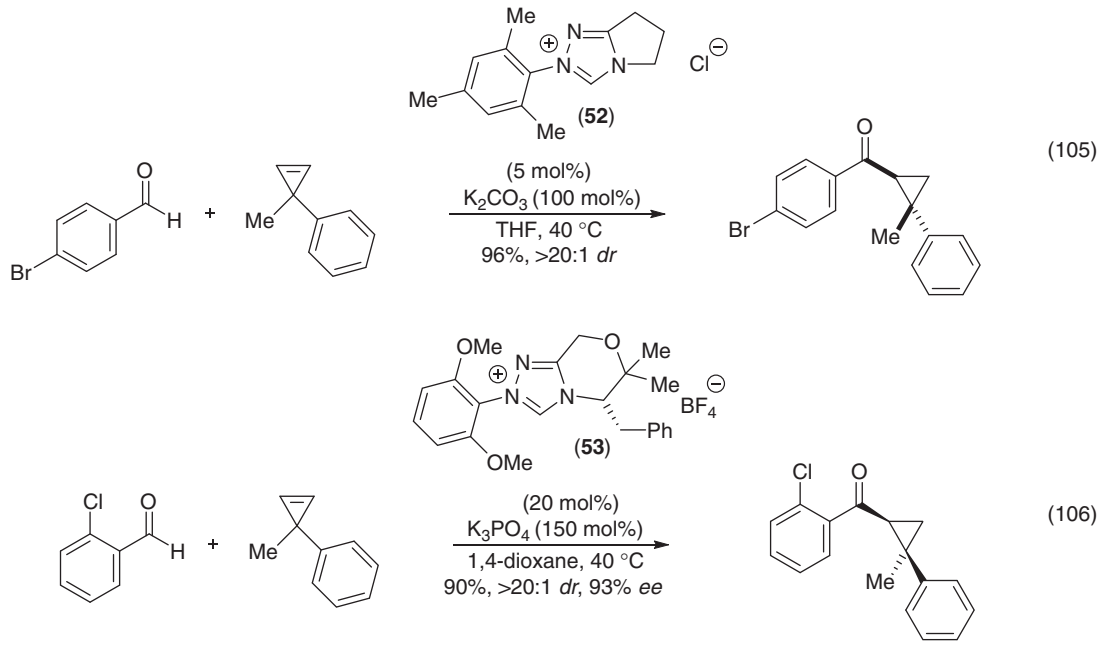
Scheme 45 Enantioselective NHC-catalyzed intramolecular alkene hydroacylation.

The levels of enantioselection achieved in these transformations were exceptional, being generally above 99%, and were attributed to the involvement of the previously proposed concerted mechanism. Good variation of the substitution pattern on both the arene-ring of the aldehyde (equations 102–104), and of the arene-ring located on the alkene (see equation 104), was possible.

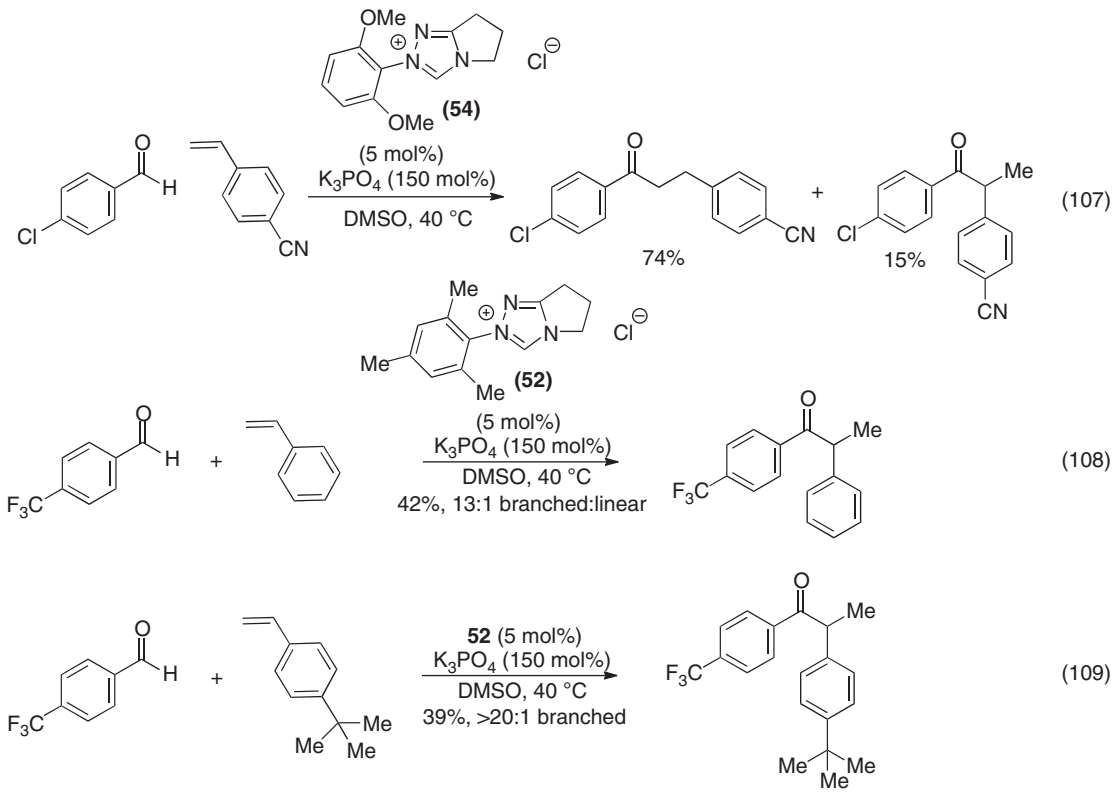
4.17.4.2 Intermolecular Reactions

The first examples of organocatalytic intermolecular hydroacylation reactions relied on the use of strained cyclopropenes to deliver the required reactivity. The carbene generated from *N*-mesityl triazolium salt **52** was found to promote the addition of a broad range of aromatic aldehydes to disubstituted cyclopropenes in good yields (equation 105, Scheme 46).[154] High levels of diastereoselection were also observed. D-Labeling studies established that the process proceeds via a *syn*-addition, which lends further support to the proposed concerted reaction mechanism. Control of the absolute stereochemistry of these intermolecular reactions could also be achieved if the carbene derived from triazolium **53** was employed as the catalyst (equation 106).[155] The strongly electron-donating methoxy substituents on triazolium **53** were found to be crucial in achieving acceptable levels of both reactivity and enantioselectivity in the desired desymmeterization reactions. Again, although limited to aryl aldehydes, use of a good range of substituents was possible on the arene core.

In 2013, the first examples of NHC-catalyzed intermolecular hydroacylation reactions of styrenes were reported. Glorius and coworkers were able to promote the addition of aromatic aldehydes to styrenes bearing an electron-withdrawing substituent, in moderate to good yields (equation 107).[156] Achiral triazolium salt **54**, featuring an electron-rich *N*-aryl substituent, was found to be the optimal catalyst, and allowed a broad range of aryl aldehydes be employed effectively. The reactions were generally linear-selective, although significant amounts of the branched isomers were also isolated in specific examples. The authors observed that the regioselectivity of these reactions depended on the electronic character of the aldehydes, with electron-rich aldehydes providing good linear selectivity, whereas electron-rich aldehydes generally provided a mixture of linear and branched adducts. Provided the styrene reaction component featured an electron-withdrawing substituent, a variety of functional groups and substitution patterns were tolerated. Significantly, the group was also able to show low levels of reactivity with styrene itself, obtaining addition products in 42% yield, provided an excess of the alkene was employed. Using these same conditions, electron-rich styrenes were investigated and also delivered low yields of the desired addition products. Interestingly, the electron-rich and electron-neutral styrene derivatives showed almost complete branch selectivity (equations 108 and 109; Scheme 47).



Scheme 46 NHC-Catalyzed intermolecular cyclopropene hydroacylation.



Scheme 47 NHC-Catalyzed intermolecular hydroacylation of styrenes.

4.17.5 Conclusions

As the preceding pages have demonstrated, there now exists a wide range of catalyst and substrate combinations that will deliver alkene, alkyne, or allene hydroacylation products. Given the wide range of substrates that can be employed, it is perhaps not

surprising that there is no single catalyst class that is universal. However, that there are so many different catalyst possibilities does suggest that there are still limitations with all of the methods that have been developed. Transition metal catalyzed reactions represent the largest class of hydroacylation reactions, and within this, transformations that employ some form of chelation control have arguably been the most successful. Despite the inherent limitation of a chelation-control strategy – that the coordinating group must be present in both substrate and product – this approach has the broadest substrate scope, in terms of aldehyde and C–C coupling partner, and has also allowed regioselective and enantioselective reactions to be developed. Nonchelation-mediated metal catalyzed approaches are promising in terms of removing the need for a chelating group, but at the present time are limited in the scope of the C–C multiple-bond coupling partners that can be employed. The majority of the radical-mediated hydroacylation reactions that have been reported rely on the use of an activator and/or catalyst, and again there is not a single combination that is general. An excess of the aldehyde reaction partner is frequently employed. The recent work on NHC-catalyzed hydroacylation reactions looks very promising, but at present the substrate scope is still limited to a relatively small class of substrates.

The first edition of Comprehensive Organic Synthesis, published in 1991, did not contain a chapter on alkene, alkyne, or allene hydroacylation. The inclusion of the relevant chapter in the second edition is testament to the significant development that has occurred in hydroacylation chemistry during the intervening years. This expansion of the hydroacylation process is no doubt fueled by the inherent features of the reaction that makes it so attractive; a simple addition process, which is necessarily atom-economic, that delivers synthetically useful carbonyl-containing products. The coming years will surely see a number of remaining limitations successfully addressed.

For related chapters in this Comprehensive, you can refer to – Chapters 3.22. 4.12, and 4.23.

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4.18 Hydroformylation and Related Carbonylation Reactions of Alkenes, Alkynes, and Allenes

B Breit and L Diab, Albert-Ludwigs-Universität Freiburg, Freiburg i. Brsg., Germany

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Glossary

Hydrometallation The addition reaction of a metal hydride to a double bond (or triple bond) to form an organometallic compound.

Protodesilylation Any substitution reaction in which a silyl group is replaced by a hydrogen atom.

Regiocontrol The formation of one regioisomer to a greater extent than others in a chemical reaction.

Stereoinduction The stereocontrol of a reaction as a result of a chiral feature present in the substrate, reagent, catalyst, or environment.

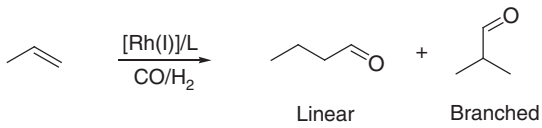
Syngas The name given to a gas mixture that contains varying amounts of carbon monoxide and hydrogen.

TOF or turnover frequency Is used to refer to the turnover per unit time, or number of molecules reacting per active site in unit time.

4.18.1 Introduction

The hydroformylation of alkenes is one of the most important applications of homogeneous catalysis in industry. Its intrinsic atom-economic nature and the use of cheap feedstocks render this process particularly attractive for the production of commodities with propene to butanal hydroformylation being volume wise the largest application (approximately 9 million tons per year).[1] Additionally, the reaction is highly attractive from a synthetic point of view since a CH and a CC bond are formed with concomitant introduction of a synthetically valuable aldehyde function. This allows for subsequent manifold skeleton-expanding operations, which may even be achieved in one-pot sequential transformations. Hydroformylation has been investigated in the synthesis of more complex molecules for many years, but due to the difficulty in controlling all aspects of reaction selectivity simultaneously, the true potential of the reaction has not yet been fully exploited. This situation is beginning to change, since the past two decades have seen some significant developments in the design of linear-selective catalysts,[2] more reactive catalyst systems,[3] tandem procedures using hydroformylation,[4,5] and the discovery of new effective chiral ligands for asymmetric hydroformylation.[1,6–14] These improvements result in the sort of levels of selectivity that make this reaction of immediate potential in academic and industrial-scale organic synthesis.

The hydroformylation of alkenes has been originally discovered by Otto Roelen in 1938,[15] and among the many transition metal complexes which have obligatory the general composition $H_xM_y(CO)_zL_n$ and catalyze this transformation the most important are cobalt and rhodium complexes.[16] Early work has focused on unmodified cobalt catalysts which, in general, require more drastic reaction conditions. Typical side reactions are hydrogenation and/or alkene isomerization. In this respect, advantageous are ligand-modified rhodium(I) catalysts which are in most cases highly chemoselective.[17–20] Additionally, the rhodium catalysts show fast rates, and high turnover numbers under mild conditions, which renders them the preferred catalysts for industrial and laboratory applications.



(1)

Hydroformylation of alkenes

A wide range of functional groups has been found to be compatible with the reaction conditions of hydroformylation (Figure 1). Among those are sensitive and reactive functional groups such as aldehydes, unprotected hydroxy and carboxylic acid functions, alkyl halides, and tosylates.[21]

The rate of alkene hydroformylation depends most significantly on the substitution pattern of the alkene. The order of alkene reactivity has been determined for unmodified cobalt and rhodium catalyst but reflects also the situation for ligand-modified rhodium catalysts (Figure 2).[22,23] The least-reactive systems that undergo hydroformylation are internally branched alkenes, i.e., trisubstituted derivatives. Furthermore, cycloalkenes are less reactive than acyclic alkenes. Tetrasubstituted alkenes are virtually inert toward hydroformylation.

Additionally, a reactivity study of Wilkinson's hydroformylation catalyst $[HRh(CO)(PPh_3)_3]$ against a diverse set of alkenic substrates gave valuable information on relative reactivities (Table 1).[18,24]

4.18.1.1 Mechanism

The mechanism of the hydroformylation has been intensively studied and is depicted in Scheme 1.[25–27] Thus, starting from different Rh(I)-sources under syngas pressure and in the presence of donor ligands L such as phosphorus-donor ligands and carbon monoxide, trigonal bipyramidal complex **1** is formed as a key intermediate. Dissociation of a carbon monoxide ligand generates the coordinatively unsaturated 16 valence electron complex **2** (I). The main catalyst cycle starts with the coordination of the alkene substrate **3** to give the trigonal bipyramidal hydrido alkene complex **4** (II) with the alkene occupying an equatorial position. This step is followed by the alkene insertion into the Rh–H bond (III, hydrometallation) to form isomeric tetragonal alkyl-rhodium complexes **5** and **10**, respectively. Subsequent coordination of carbon monoxide (IV) yields trigonal

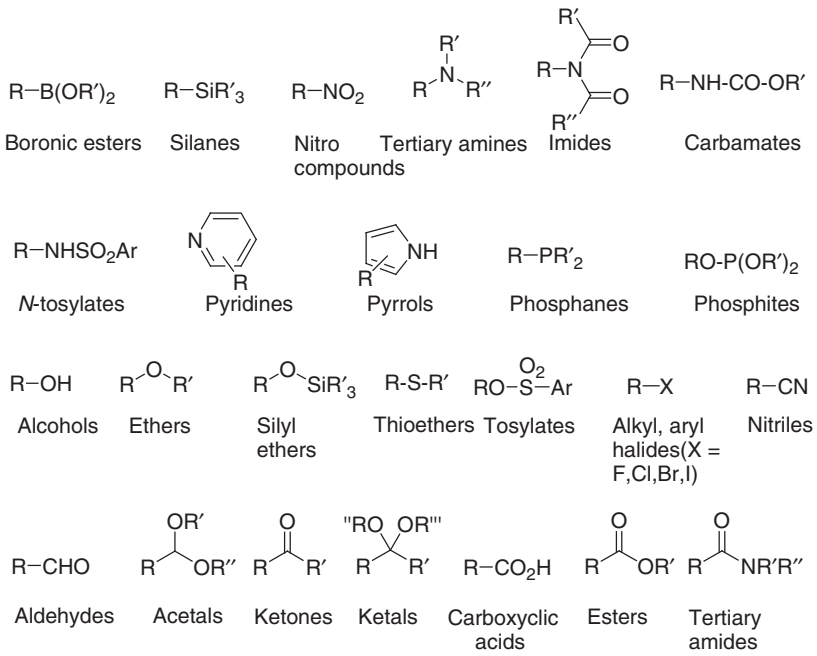


Figure 1 Functional groups compatible with the conditions of the hydroformylation conditions.

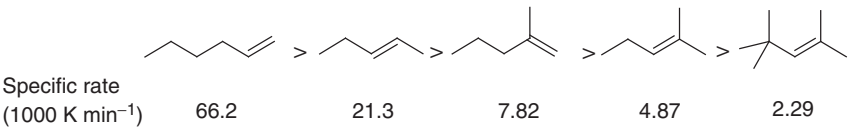
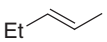
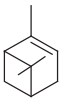
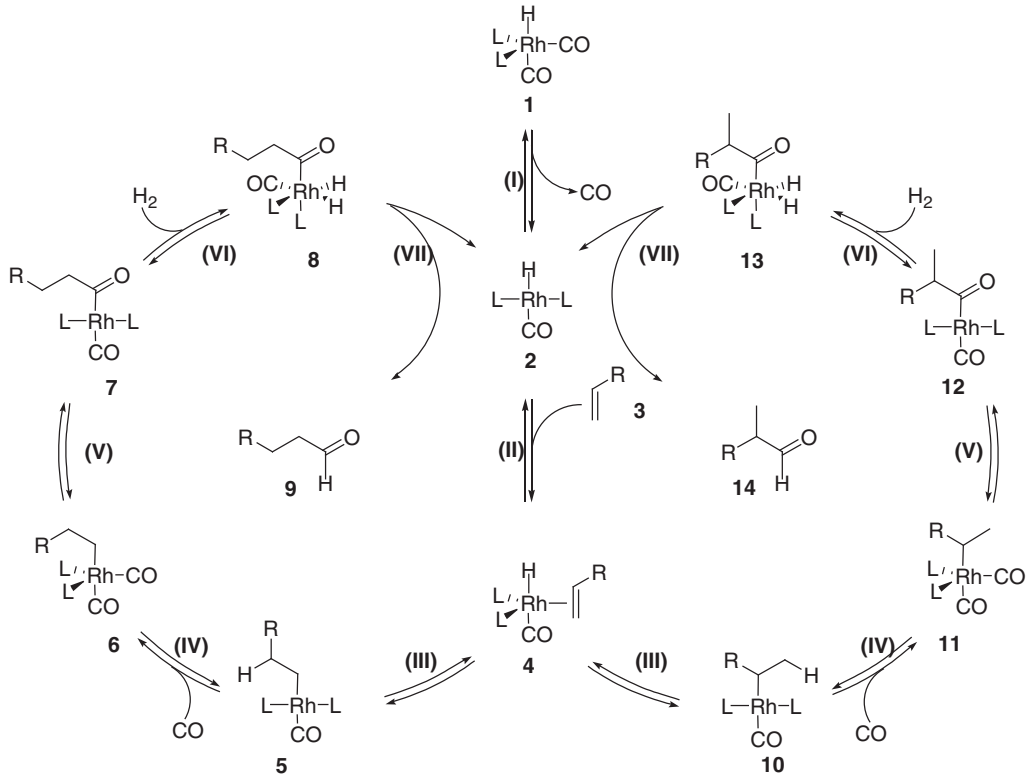


Figure 2 Effect of alkene substitution pattern on hydroformylation rate.

Table 1 Relative rate for the hydroformylation of different alkenes employing Wilkinson's hydroformylation catalyst

No.	*Alkene*	*Relative rate*
I		4.32
II		3.73
III		3.50
IV		0.15
V		0.15
VI		0.12
VII		0.06
VIII		<0.05
IX		<0.05

bipyramidal complexes **6** and **11**, respectively, which set the stage for migratory insertion of the alkyl substituent to one of the coordinated carbon monoxide ligands (V) to form the tetragonal acyl complexes **7** and **12**. Finally, oxidative addition of dihydrogen (VI, **8**, **13**) followed by reductive elimination (VII) liberates the isomeric aldehydes **9** and **14** and regenerates the catalyst **2** (Scheme 1).



Scheme 1 Current mechanistic description for the rhodium-catalyzed hydroformylation of alkenes.

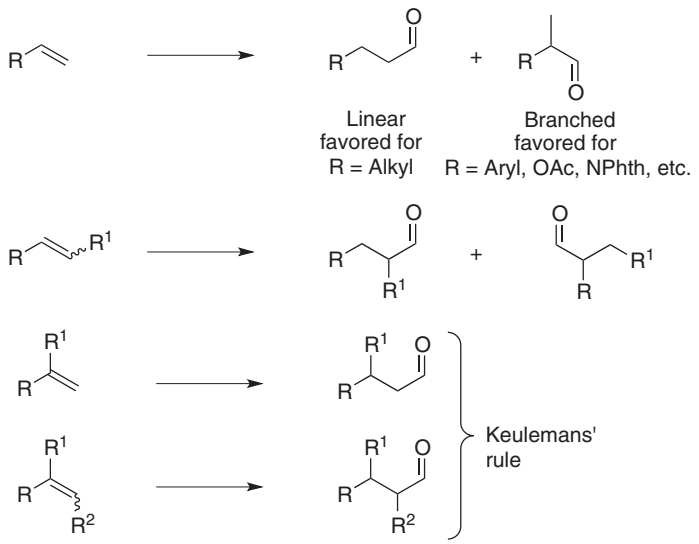
Kinetic studies performed with the triphenylphosphine-modified rhodium catalyst indicate that even for sterically less-demanding alkenes such as ethylene and propene, the rate-determining step is early in the catalytic cycle, and this may be either the alkene addition or insertion step. Deuterioformylation experiments employing a rhodium-diphosphine catalyst and 1-hexene as the substrate have shown that alkene insertion into the Rh–H bond is irreversible with respect to the formation of the linear alkyl-Rh-species **5**.[28,29] However, this step III may become reversible for the formation of the branched alkyl-rhodium species **10** which depends on the reaction conditions; the nature of the alkene and the catalyst.

4.18.2 Regioselectivity

Regioselectivity on hydroformylation of alkenes is a function of many factors. These include inherent substrate preferences, directing effects exerted by functional groups and finally the effects induced by the catalyst. Most efficient are regiocontrol effects based on tailor-made ligands which craft the accessible space at the catalytically active metal center. In order to understand substrate-inherent regioselectivity trends, the four classes of alkenes have to be discussed separately: terminal alkenes, 1,2-disubstituted alkenes, 1,1-disubstituted, and trisubstituted alkenes.[30] The issue of regioselectivity usually only arises for terminal and 1,2-disubstituted alkenes. For alkyl-substituted terminal alkenes there is a slight preference for the linear product. For terminal alkenes containing electron-withdrawing substituent the formation of the branched product is favored, and is sometimes the exclusive product. This tendency is more or less unaffected by the catalyst structure. Both 1,1-disubstituted and trisubstituted alkenes, in general, provide only one regioisomeric product based on Keulemans′ rule which states that the formyl group is attached such as to avoid the formation of a quarternary carbon atom (Scheme 2).[31]

Good solutions exist now for the preferred formation of the linear aldehydes on hydroformylation of terminal alkenes; the formation of the branched aldehyde, in particular, for simple alkyl-substituted alkenes is an unsolved problem. Even more difficult is the regiocontrol on hydroformylation of 1,2-unsymmetrically disubstituted alkenes.

In the following discussion the reactions will be classified by degree of substitution at the alkenic substrate. For each class, the authors will focus on substrate control, this will include steric and electronic effects as well as substrate-directed regioselective hydroformylations and catalyst control where the most important catalyst developments for catalyst-based regiocontrol will be discussed.



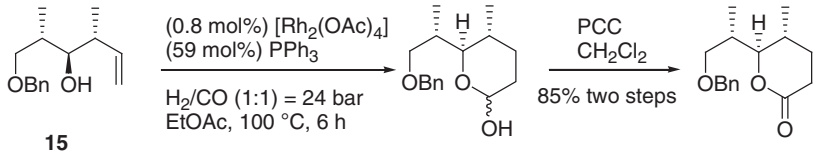
Scheme 2 Regioselectivity trends on hydroformylation of different alkene classes.

4.18.2.1 Terminal Alkenes

4.18.2.1.1 Linear-regioselective hydroformylation

4.18.2.1.1.1 Substrate control

Monoalkyl-substituted terminal alkenes have a slight preference to form the linear aldehyde on hydroformylation while employing standard catalysts such as rhodium/triphenylphosphine. This regiochemical preference for the linear isomer may be enhanced if the alkene substituent is a secondary or tertiary alkyl group. As an example, the hydroformylation of homoallylic alcohol **15** is shown (Scheme 3). Here, complete regioselectivity in favor of the linear aldehyde was obtained.



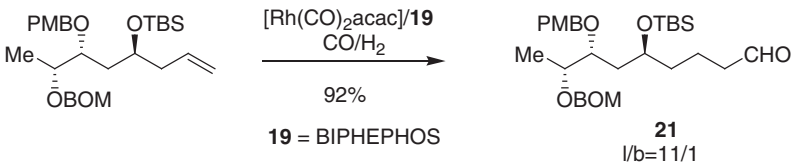
Scheme 3 Regioselective hydroformylation of C3-branched alkyl-substituted terminal alkenes.

4.18.2.1.1.2 Catalyst control

Much progress has been made to address the issue of regioselective hydroformylation of terminal alkenes in favor of the linear product by using rhodium catalysts that are modified by mono- and bidentate ligands. In particular, bidentate diphosphine and diphosphite ligands, which have a natural bite angle of approximately 110°, will favor the linear product. The most successful ligand types are BISBI **16**,[32] BIPHEPHOS **19**,[33] XANTPHOS systems **18**,[34] Naphos **17**,[35] α-calix[4]arene diphosphite,[36] and pyrrole-based bisphosphoramidites (Figure 3).[37]

The rhodium(I)/BIPHEHOS and rhodium(I)/XANTPHOS catalysts have been proven reliable catalysts systems for a wide range of terminal olefins to furnish the linear aldehydes. It has even been applied in total synthesis as well as a key step for tandem processes.[38,39]

Two recent examples are shown below. The hydroformylation of an aldehyde allylation product has served as a key step for the preparation of a BC-ring subunit **21** of the anticancer agent bryostatin (equation 2).[38]



(2)

An interesting one-pot hydroformylation/Fischer-Indole sequence can be achieved running the hydroformylation in the presence of a phenylhydrazine **22** (equation 3). This protocol gave access to the methyl ester **23** of the plant growth regulator 3-indole butanoic acid (IBA).[39]

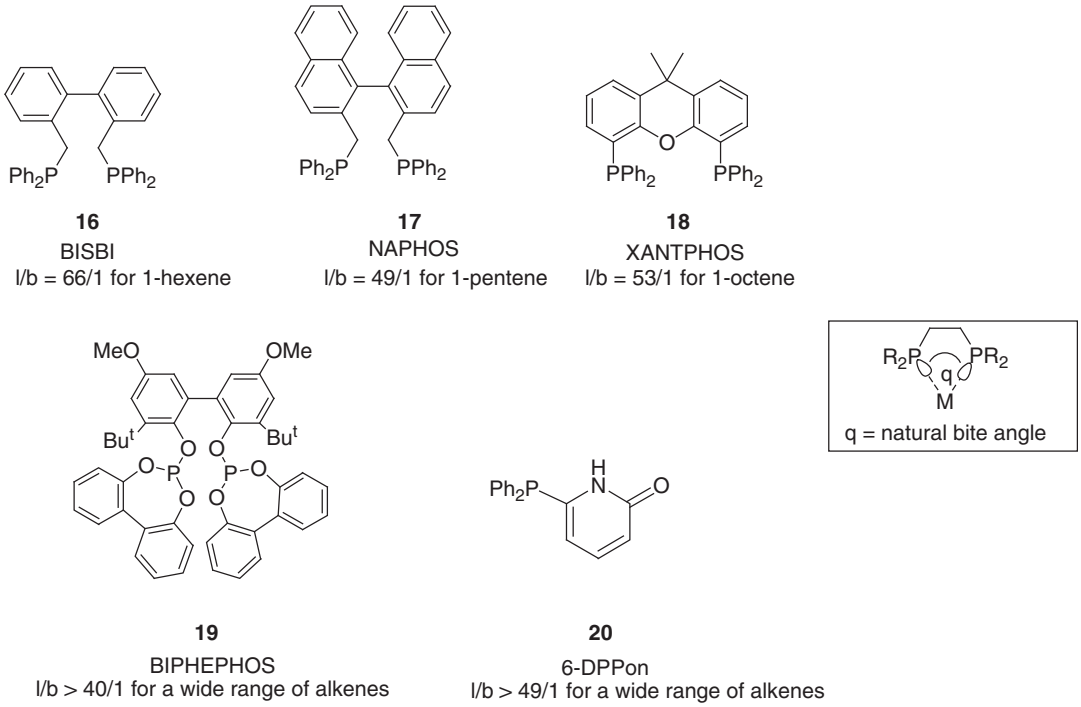
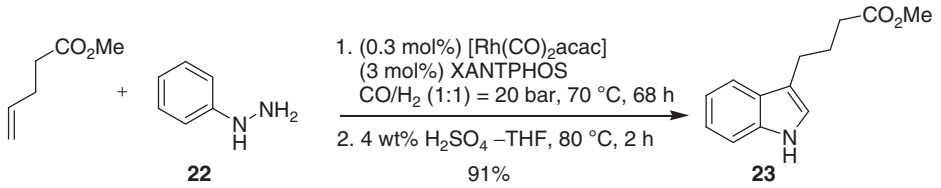
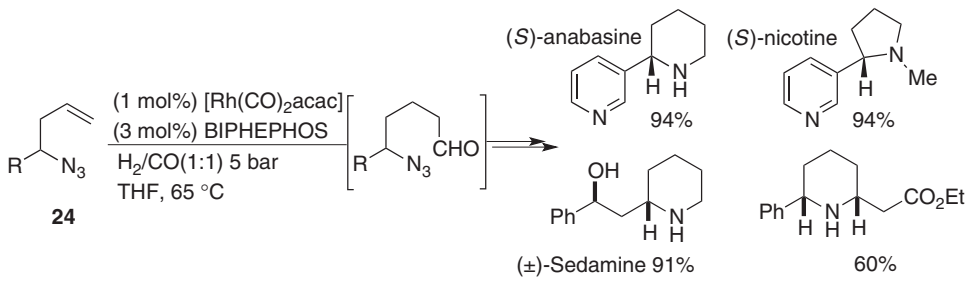


Figure 3 Bidentate ligands for regioselective hydroformylation of terminal alkenes.



(3)

Interestingly, the reduced nucleophilicity of the phosphite donor (BIPHEPHOS) compared with a phosphine donor allowed applying this ligand system for the hydroformylation of homoallylic azides **24**. Phosphine ligands such as XANTPHOS do fail in this case since they react with the azide by way of a Staudinger reaction. The hydroformylation of homoallylic azides **24** followed by one-pot subsequent transformations such as (hydrogenation/Wittig olefination/Staudinger reaction/Michael addition/Schmidt rearrangement) served as the key step for the preparation of several piperidine- and pyrrolidine-containing alkaloids in good yields (Scheme 4).[39]



Scheme 4

A particularly active and regioselective rhodium catalyst provides the monophosphine ligand 6-DPPon **20** which self-assembles in the coordination sphere of the rhodium metal center with its own tautomeric hydroxypyridine to give a bidentate diphosphine ligand through hydrogen bonding (Figure 4).[40]

This system allows for room-temperature, ambient-pressure, and regioselective hydroformylation of terminal alkenes and is compatible with a number of functional groups, even those capable of hydrogen bonding (Table 2).

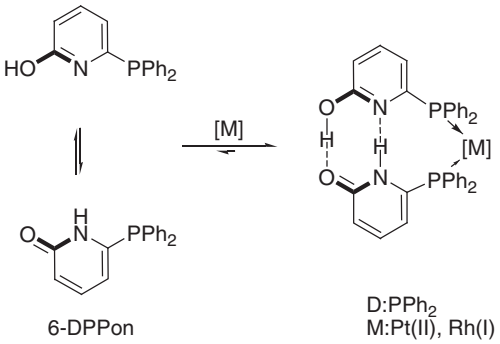
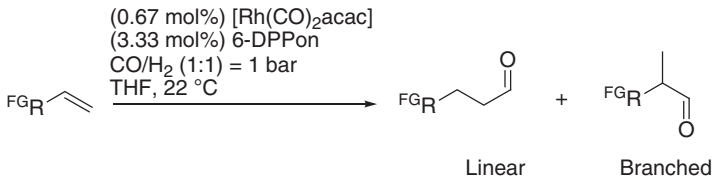
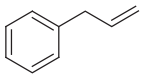
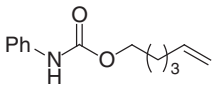
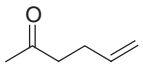
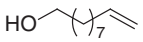
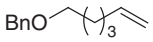
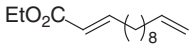
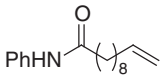
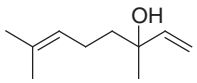


Figure 4 The self-assembling 6-diphenylphosphinopyridin-2-(1H)-one (6-DPPon; **20**) ligand system.

Table 2 Result of room-temperature/ambient-pressure hydroformylation of functionalized terminal alkenes with rhodium/6-DPPon catalyst



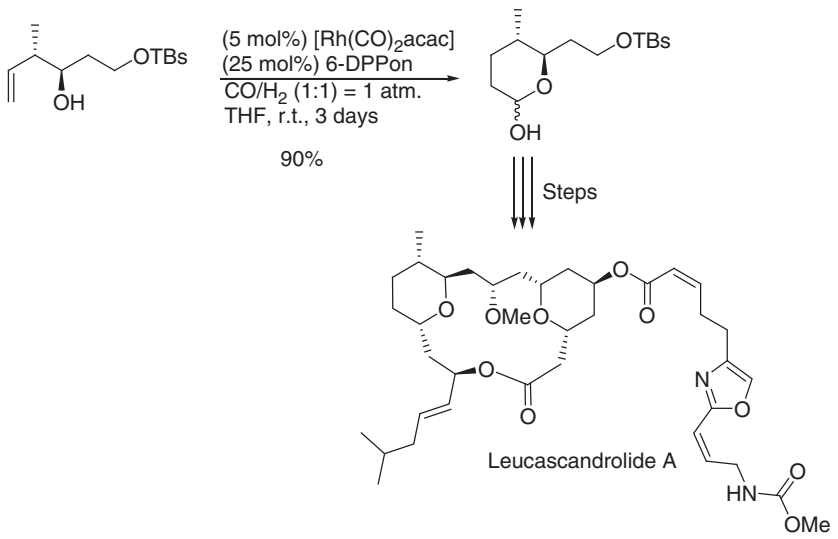
No.	*Substrate*	*l/b*	*Isomerization (%)*[a]	*Time (h)*	*Yield (%)*
I		99/1	5	20	>95
II		91/9	<4	20	90
III		98/2	4	20	98
IV		99/1	5	20	88
V		99/1	5	20	98
VI		97/3	5	20	99
VII		91/9	9	85	88
VIII		99/1	5	20	65
IX		99/1	–	20	>95
X		99/1	<4	20	>95

[a]Formation of mixtures of internal alkene isomers through double-bond migration which are not further hydroformylated under these conditions.

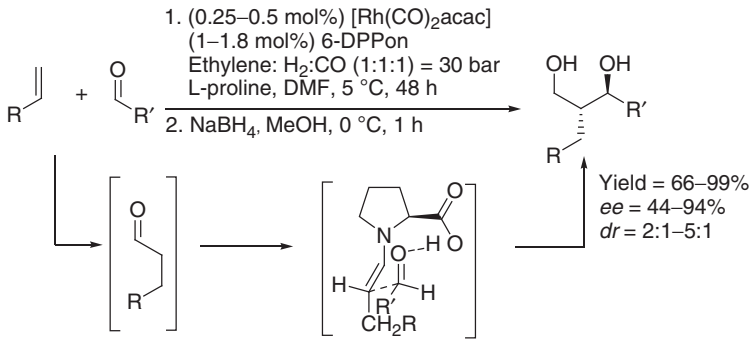
This catalyst has proven its reliability during a recent synthesis of the cytotoxic and antifungal macrolide Leucascandrolide A (Scheme 5).[41]

The Rh(I)/6-DPPon catalyst was also applied to achieve a domino hydroformylation/enantioselective cross-aldol addition (Scheme 6). Here the advantage of this catalyst system is its exceptional activity even at low temperatures which on combination with organocatalysis is crucial to achieve high diastereo- and enantioselectivity in the course of the aldol step.[41]

Recently, a new class of tetraphosphane ligands **25** based on a biphenyl backbone has emerged. Rhodium catalysts derived from these ligands displayed high regioselectivity on hydroformylation of terminal alkenes even at high temperatures (Table 3).[42] It could also be applied to achieve a highly linear-regioselective hydroformylation of 1,5-hexadiene. The linear dialdehyde is a valuable

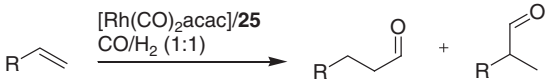


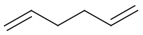
Scheme 5

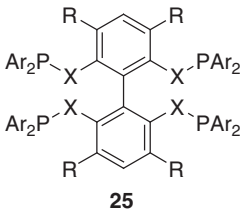


Scheme 6 Design of a domino hydroformylation/organocatalytic cross-aldol reaction.

Table 3 Tetra phosphane ligands **25** for linear-selective hydroformylation



No.	*Substrate*	*Conditions*	*L*	*Isomerization (%)*	*Yield (%)*	*l/b*
I		0.05 mol% [Rh(I)], 100 °C, 20 bar, toluene, 1 h	**25a**	4.2	–	99.2/0.8
II		0.05 mol% [Rh(I)]), 120 °C, 20 bar, toluene, 1 h	**25d**	4.5	–	98.5/1.5
III		0.1 mol% [Rh(I)], 100 °C, 80 bar, toluene, 2 h	**25g**	<1	78	98.3/1.7
IV	Ph	0.01 mol% [Rh(I)], 80 °C, 10 bar, toluene, 12 h	**25f**	–	91	95.5/4.5
V	*m*-MeC$_6$H$_4$	0.01 mol% [Rh(I)], 80 °C, 10 bar, toluene, 12 h	**25f**	–	90	99.3/0.7



25

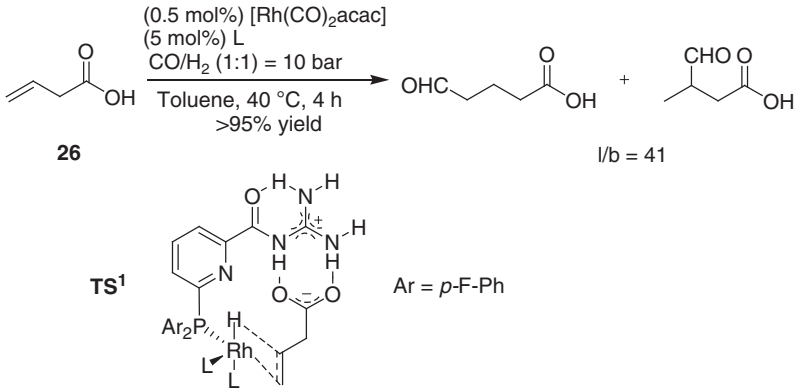
25a: Ar = 3,5-difluorophenyl, R = H, X = CH_2
25b: Ar = *p*-CF_3Ph, R = H, X = CH_2
25c: Ar = *p*-MePh, R = H, X = CH_2
25d: Ar = *m*-CF_3Ph, R = H, X = CH_2
25e: Ar = 3,5-difluoromethylphenyl, R = H, X = CH_2
25f: Ar = *N*-pyrrolyl, R = Tolyl, X = O
25g: Ar = *N*-pyrrolyl, R = Et, X = O

intermediate for the preparation of various important products such as bicarboxylic acids,[43] diamines,[44] heterocyclic compounds,[45] or could act as cross-linking agents for polymers such as proteins and other functionalized macromolecular compounds.[46]

Styrenes are an interesting class of substrates since for electronic reasons the formation of the branched aldehyde is favored. However, recently it has been found that it is possible to overrule the intrinsic branched-selective hydroformylation of styrene by the choice of solvent,[47] the application of a biphasic reaction system,[48] employing a different metal catalyst system[49] ($PtCl_2$/$SnCl_2$, l/b = 3.35, for Co–W bimetallic system l/b = 1.3) or by catalyst control, using special ligands.[50–52] So far, the highest selectivity toward the linear aldehyde was obtained using a rhodium catalyst derived from the 3,3′,5,5′-substituted tetraphosphorus ligands **25** (Table 3).[53]

All previously discussed catalyst systems achieved selectivity via disfavoring the hydrometallation transition state toward the branched isomer applying repulsive steric interactions between catalyst and substrate.

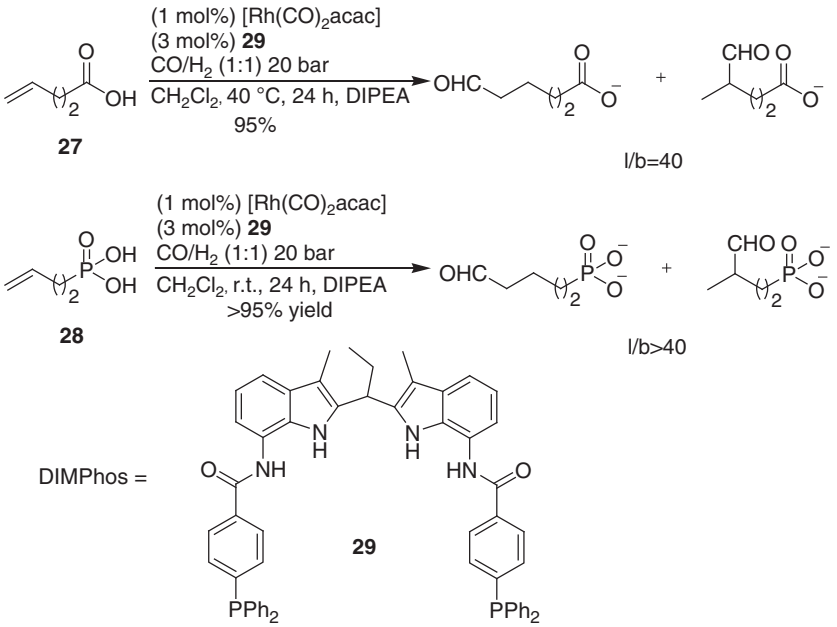
Conversely, recently new supramolecular catalyst systems have been developed which operate enzyme-like through additional hydrogen-bonding interactions between catalyst and substrate. Transition state TS^1 stabilization toward the linear aldehyde has been found as the origin of selectivity. An example for this type of supramolecular catalyst is the acylguanidinium-functionalized monophosphine. The additional guanidine function has been shown to be essential to give superior activity, predictable regiocontrol, and substrate selectivity on hydroformylation of vinyl acetic acid (**26**) (equation 4).[54]



(4)

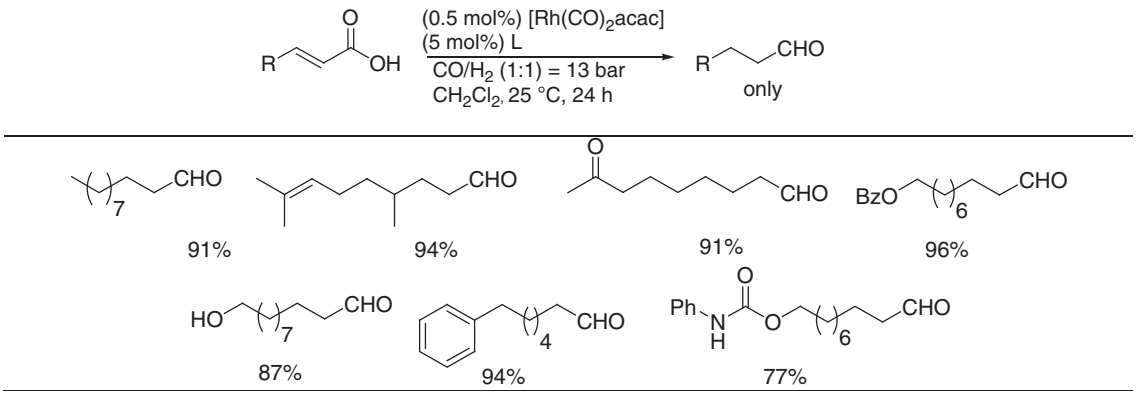
Regioselective hydroformylation of unsaturated carboxylic acids

A similar strategy has been described using a new bidentate phosphorus ligand with an integral anion recognition site **29** (DIMPhos) (Scheme 7). Indeed, high regioselectivity for the linear aldehyde was observed for the ω-unsaturated carboxylic acid **27** and phosphonic acid **28**.[55]



Scheme 7 Regioselective hydroformylation of ω-unsaturated carboxylic acids and phosphinic acids.

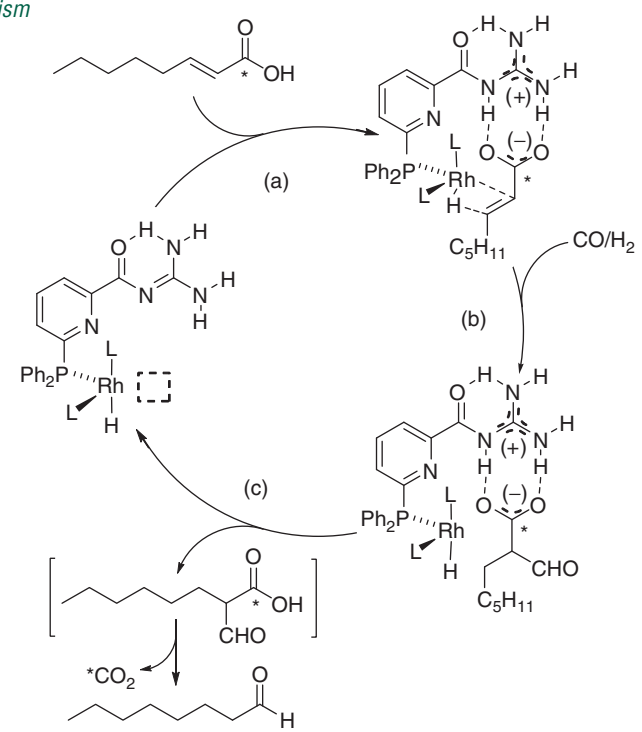
A unique supramolecular ligand substrate interaction enabled the first decarboxylative hydroformylation of α,β-unsaturated carboxylic acids to give linear aldehydes in very high regioselectivity up to 99/1 (Scheme 8). This is a formal 4H reduction which lacks any precedence in the literature. The carboxy function serves formally as a traceless directing group for the introduction of the aldehyde function in the α-position and is subsequently removed by decarboxylation. This reaction proceeds under mild conditions, tolerates a variety of functional groups (hydroxyl, ketone, dialkylsulfide, ether, ester internal double bond, and acetal) and liberates CO_2 as the only stoichiometric byproduct.[56]



Scheme 8

The proposed reaction mechanism involves a carboxylate/guanidinium interaction of the ligand with the substrate. This decreases the electron-withdrawing character of the carboxylic acid function which in turn allows for chemo- and regioselective hydroformylation. A final decarboxylation delivers the saturated aldehyde. Labeling experiments with 13C-labeled substrate shows complete loss of the 13C label in the product which is in agreement with the proposed mechanism.

4.18.2.1.1.3 Proposed mechanism



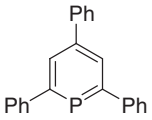
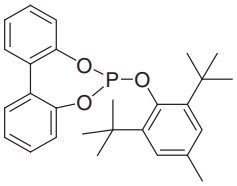
4.18.2.1.2 Branched-regioselective hydroformylation

Branched-regioselective hydroformylation relies so far primarily on substrate control. This control can be passive (electronic and steric effects) or active (additional attractive interactions between catalyst and the substrate through directing groups).

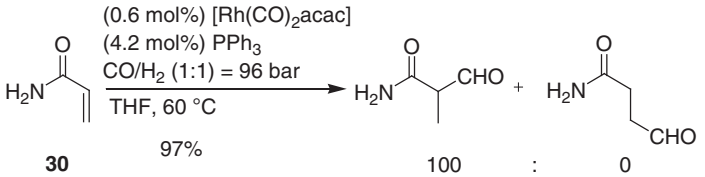
4.18.2.1.2.1 Passive control

Alkenes possessing an aryl or electron-withdrawing substituent such as vinyl acetate, vinylphthalimide, acrylic esters, vinyl sulfones, and sulfoxides as well as fluorine-substituted derivatives can be regioselectively hydroformylated and show, in general, a strong preference for the formation of the branched product (Table 4). It has been suggested that the origin of the selectivity is the formation of a η^3-benzyl complex that stabilizes the branched rhodium alkyl intermediate.[57] However, since electron-poor alkenes lead also to the branched isomer, this suggests that the origin of this regioselectivity may stem from a higher stability of the metal–Cα bond (formed on alkene insertion) compared with the alternative metal–Cβ bond because of substantial stabilization of the formal negative charge developing at α-carbon. Whatever is the origin of the regioselectivity in hydroformylation of aryl alkenes, a considerable number of phosphine-based rhodium catalysts will deliver the branched aldehyde with acceptable to high regioselectivity and chemoselectivity.

Table 4 Branched-selective hydroformylation of 2-functionalized terminal alkenes

No.	R	Conditions	Ligand	Ratio (b/l)	Conversion (%)	References
I	Ph	$[Rh(CO)_2acac]$, 90 bar, 30 °C, 16 h	–	97/3	99	58
II	Ph	$[Rh(cod)]^+BF_4^-$, 14 bar, 47 °C, 22 h	–	98/2	89	59
III	Ph	$[Rh(CO)_2acac]$, 20 bar, 25 °C, 22 h		95/5	>99	60
IV	Ph	$[Rh(CO)_2acac]$, 90 bar, 30 °C, 16 h	PPh_3	96/4	31	60
V	OAc	$[Rh(cod)(OAc)]_2$, 60 bar, 20 °C, 22 h	–	99/1	>95	61
VI	CF_3	$[Rh_{14}(CO)_{12}]$, 110 bar, 80 °C, 6 h	–	97/3	98	62
VII	CO_2Et	$[Rh(CO)_2acac]$, 50 bar, 50 °C, 1.75 h	PPh_3	99/1	>99	63
VIII	SO_2Ph	$[Rh(cod)]^+BF_4^-$, 40 bar, 75 °C, 22 h	dppb	99/1	94	64
IX	*N*-Phth	$[Rh(CO)_2acac]$, 20 bar, 80 °C, 0.7 h		99/1	100	65

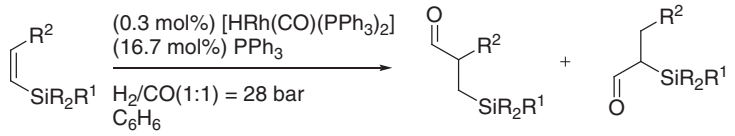
New applications for substrate-controlled branched-selective hydroformylation of alkenes substituted with electron-withdrawing substituents have emerged. A recent example is the hydroformylation of acrylamide **30** with a standard rhodium/triphenylphosphine catalyst, which yields the branched aldehyde exclusively (equation 5).[66]



(5)

Branched-regioselective hydroformylation of acrylamide

To allow for a formal branched-regioselective hydroformylation of terminal alkyl-substituted alkenes, the temporary introduction of a bulky silicon substituent at the alkene terminus has proved useful (equation 6).[63,67] Avoidance of steric repulsion between the bulky silicon group and the rhodium catalyst is the dominant regiocontrol element. A subsequent removal of the silicon substituent through protodesilylation would liberate the branched product.

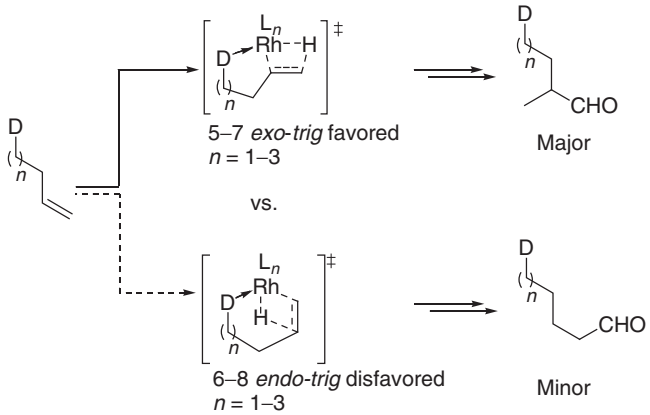


R = R^1 = Me, R^2 = Ph, T = 50 °C, b/l = 98/2
R = Ph, R^1 = R^2 = *t*-Bu, T = 80 °C, b/l = 96/4
R = Ph, R^1 = *t*-Bu, R^2 = CH_2OMe, T = 50 °C, b/l = 97/3
R = Ph, R^1 = *t*-Bu, R^2 = CH(OH)Me, T = 80 °C, b/l = 98/2 (6)

Formal branched-selective hydroformylation of terminal alkenes with the aid of a silicon control substituent

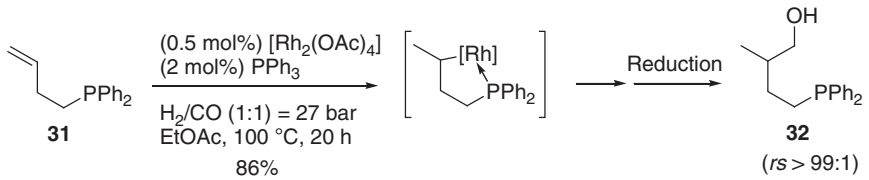
4.18.2.1.2.2 Active control

An alternative to control regioselectivity relies on active substrate-direction. This can be achieved by introducing a soft donor substituent (D) which can chelate the Rh catalyst. Insertion of the alkene can proceed through a 5–7-*exo-trig* transition state which is in all cases highly favored compared with a competing 6–8-*endo-trig* transition state for stereoelectronic reasons (Scheme 9).



Scheme 9

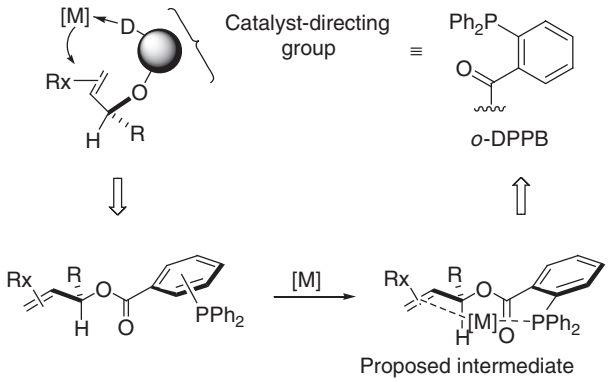
Efficient Lewis basic donor groups (D) have to effectively compete with CO as a ligand for rhodium. Hence, soft donors such as phosphines, phosphinites, and phosphites have proven useful. An early example is the phosphine-directed hydroformylation of 4-(diphenylphosphino)but-1-ene **31** (Scheme 10).[68] Complete regioselectivity in favor of the branched alcohol isomer **32** is observed which is formed by *in situ* reduction of the original aldehyde product. Conversely, hydroformylation of hex-1-ene under the same conditions gave a mixture of linear and branched aldehydes in a ratio of 75/25.[68] When a phosphite was used as the directing group, the branched aldehyde could be obtained in excellent yield.[69]



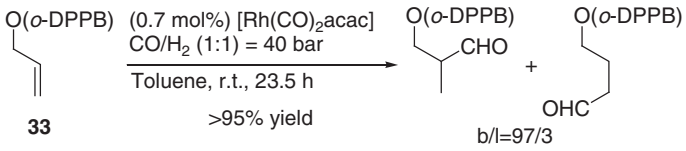
Scheme 10 Regiocontrol through active substrate-direction.

A major disadvantage of this carbon-bound phosphine-directing group is the difficulty of its synthesis and its removal from the substrate. A removable substrate-bound catalyst-directing group could be a solution. Such a group may be attached easily to e.g., an alcohol function which is present in many organic substrates. In this regard the *ortho*-diphenylphosphanyl benzoate (*o*-DPPB) function has proved to be particularly efficient for hydroformylation (Scheme 11).

Branched-regioselective hydroformylation of allylic *o*-DPPB ester **33** could be accomplished in excellent yield and selectivity (equation 7).[70] However, hydroformylation of the homologous homoallylic *o*-DPPB ester was completely regio-random (b/l = 45/42). This shows that during the selectivity-determining hydrometallation step this system can efficiently discriminate 8-*exo-trig* versus 9-*endo-trig* transition states but not 9-*exo-trig* versus 10-*endo-trig* transition states.



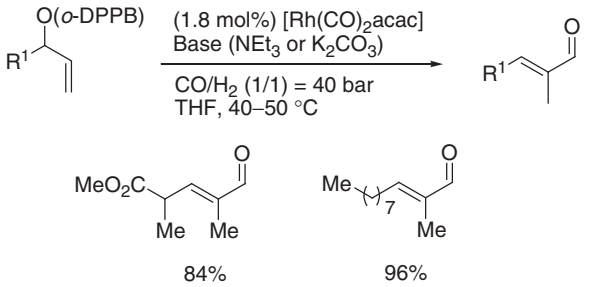
Scheme 11 Development of the catalyst-directing *o*-DPPB group.



(7)

Directed hydroformylation of allyl *o*-DPPB esters with mono-substituted alkenes

In the presence of a suitable base this directed hydroformylation can be coupled with *in situ* elimination of the directing *o*-DPPB group to furnish enals in high yields and *E*-selectivities (equation 8).[71]

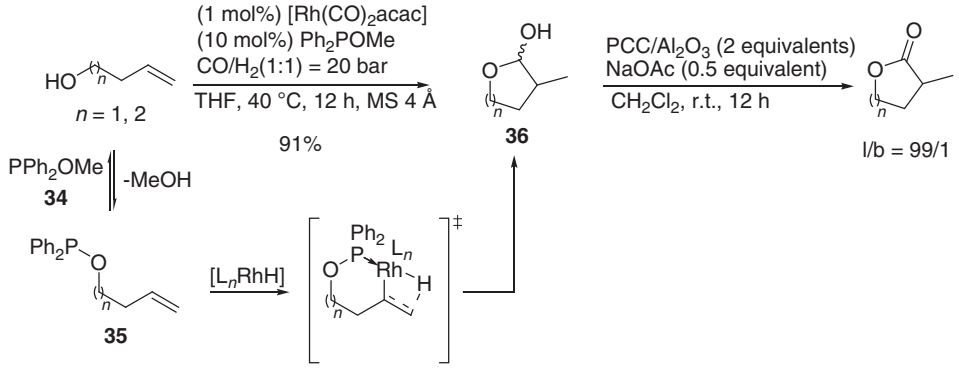


(8)

Tandem *o*-DPPB-directed hydroformylation/β-elimination of allylic esters

Though this strategy is useful, it requires stoichiometric amounts of the directing group, which has to be installed and removed in extra steps. More efficient is the use of directing groups which can bind the substrate in a covalent but reversible fashion which omits preinstallation. Furthermore, the rate acceleration provided by the directing group allows branched-selective hydroformylation to proceed with only catalytic amounts of the directing ligand.

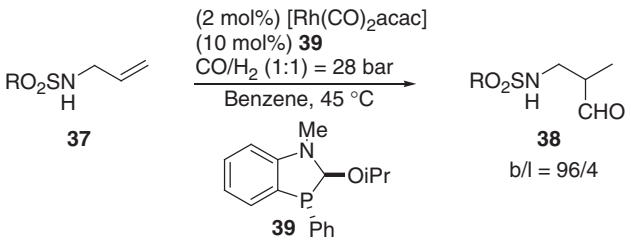
In this regard, phosphinites **34** were used as reversibly bound catalyst-directing groups for the highly branched-regioselective hydroformylation of homoallylic and bishomoallylic alcohol derivatives to obtain attractive γ- and δ-lactone building blocks (Scheme 12).[72] The first step in this reaction is the transesterification of the alcohol function by methyl phosphinite **34**, to furnish



Scheme 12 Branched-regioselective hydroformylation of homo and bisallylic alcohols with the aid of a catalytic directing group.

phosphinite **35**, which undergoes a regioselective-directed hydroformylation, favoring the 6/7-*exo-trig* versus the competing 7/8-*endo-trig* hydrometallation transition state. The lactols **36** are liberated after subsequent transesterfication with the substrate.

β-Aminoaldehydes **38** were obtained through a highly regioselective hydroformylation of sulfonamides substrates **37** which can bind to the directing ligand **39** through reversible aminal formation (equation 9).[73]



(9)

4.18.2.2 Higher-Substituted Alkenes

Increasing the number of alkene substituents results in an exponential drop of alkene reactivity which requires harsh conditions (pressure and temperature) for the hydroformylation reaction to proceed at reasonable rates. For this reason a set of *π*-acceptor monodentate ligands **40–42** has been developed giving rise to rhodium catalysts that display extraordinary activity and allow for hydroformylation of 1,1- and 1,2-disubstituted alkenes under rather mild conditions (Figure 5).[74] However, bulky monodentate phosphites **40** and phosphinines **41** have a high tendency toward alkene isomerization which makes them less useful in terms of selectivity regarding a position-selective hydroformylation of an internal alkene. Conversely, the phosphabarrelene **42** furnishes a rhodium catalyst that indeed combines very high activity with an extraordinary low tendency for alkene isomerization.[74]

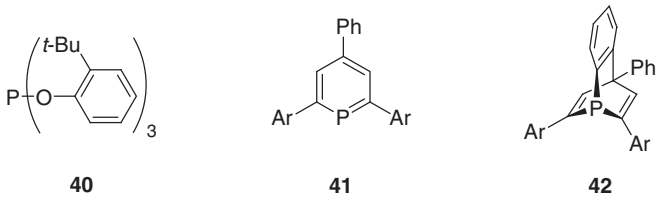
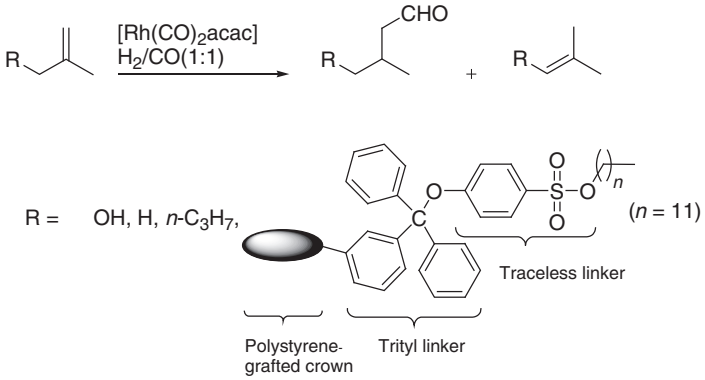


Figure 5 Ligands that provide highly active rhodium catalysts for the efficient hydroformylation of higher-substituted alkenes.

4.18.2.2.1 1,1-Disubstituted alkenes

4.18.2.2.1.1 Passive substrate control

1,1-Disubstituted alkenes strongly prefer the formation of the linear product (Keulemans' rule).[31] This rule is indeed valid for the majority of 1,1-disubstituted alkenic substrates and is operative for both, solution as well as solid-phase hydroformylation (equation 10).

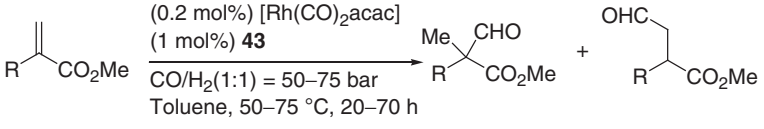


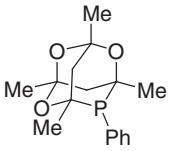
(10)

Hydroformylation of 1,1-disubstituted alkenes

Only in special cases, such as *α*,*β*-unsaturated esters, which are electronically activated to form the branched isomer, a violation of this rule has been observed. Hydroformylation of a range of 1,1-disubstituted unsaturated esters yields quaternary aldehydes (Table 5).[75]

Table 5 Results of branched-selective hydroformylation of α,β-unsaturated esters with a rhodium/phosphaadamantane **43** catalyst

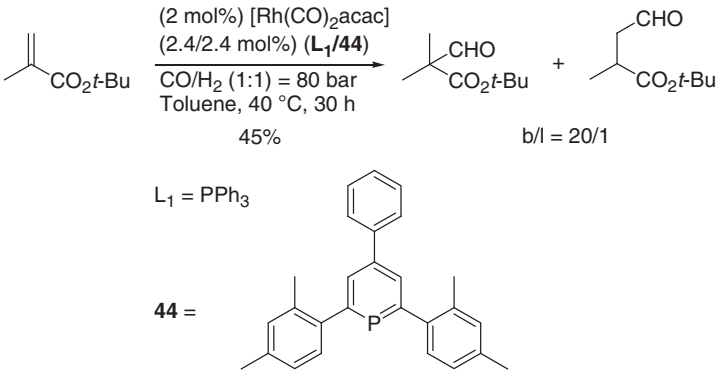




43

No.	*R*	*b/l*
I	Me	50/1
II	Ph	>100/1
III	MeO_2CCH_2	99/1
IV	$NC(CH_2)_2$	22/1
V	$MeO_2C(CH_2)_2$	56/1

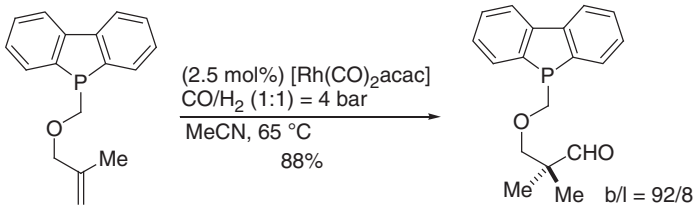
A rhodium catalyst employing a 1:1 mixture of triphenylphosphine and a monodentate phosphabenzene ligand **44** showed high regioselectivity for branched-selective hydroformylation of methacrylic esters (equation 11).[76]



(11)

4.18.2.2.1.2 Active substrate control

For 1,1-dialkylsubstituted alkenes, violation of Keulemans' rule can be achieved employing catalyst-directing groups. In this sense, the dibenzophosphol-5-ylmethyl ether **45** of methallylic alcohol provided the quaternary aldehyde in good selectivity (equation 12).[77]

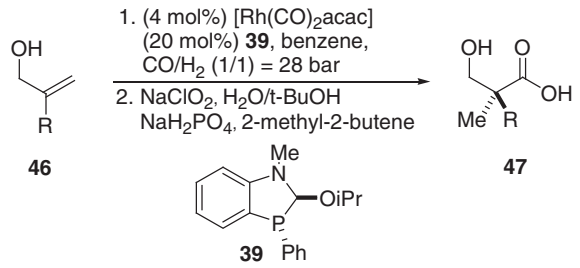


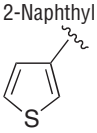
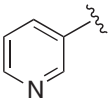
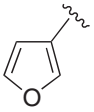
45

(12)

Alternatively, dynamic covalent directing group **39** was found to be efficient for the directed branched-selective hydroformylation of 1,1-disubstituted olefins, especially 2-aryl-substituted allylic alcohols **46**, and furnished the quaternary products in good regioselectivities, which were isolated after oxidation to the corresponding carboxylic acids **47** in good yields (Table 6).[78]

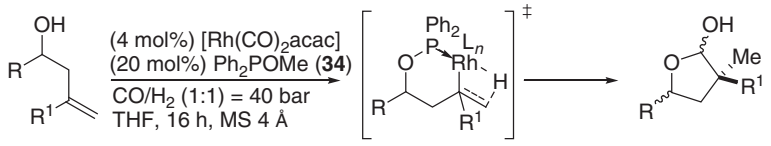
Table 6 Branched regioselective hydroformylation of 2-substituted allylic alcohols **46** with directing ligand **39**



No.	*R*	*Temperature (°C)*	p-*TsOH (%)*	*b/l*	*Yield (%)*
I	*p*-CF_3-Ph	45	0.2	96/4	85
II	*p*-OMe-Ph	35	0.2	98/2	66
III	*p*-Br-Ph	35	0.05	94/6	71
IV	*m*-Cl-Ph	35	0.2	98/2	77
V	*p*-CO_2Me-Ph	45	0.05	98/2	74
VI	2-Naphthyl	35	0.05	95/5	85
VII		45	0.2	95/5	70
VIII		45	0.2	98/2	68
IX		55	0.05	98/2	64
X	Me	45	0.2	76/24	49

Though regioselectivities are high, the methodology so far is restricted to the use of 2-aryl-substituted allylic alcohol derivatives, whereas reactions with alkyl-substituted allylic alcohol derivatives were less regioselective. In a recent study, diphenylphosphinite **34** was applied as a dynamic directing group for the highly chemo- and regioselective hydroformylation of homoallylic alcohols **48** enabling the construction of quaternary carbon centers. The synthesis of a wide range of α,α-disubstituted γ-lactols/lactones and highly substituted tetrahydrofurane derivatives was reported in good yields and regioselectivities (Table 7).[79]

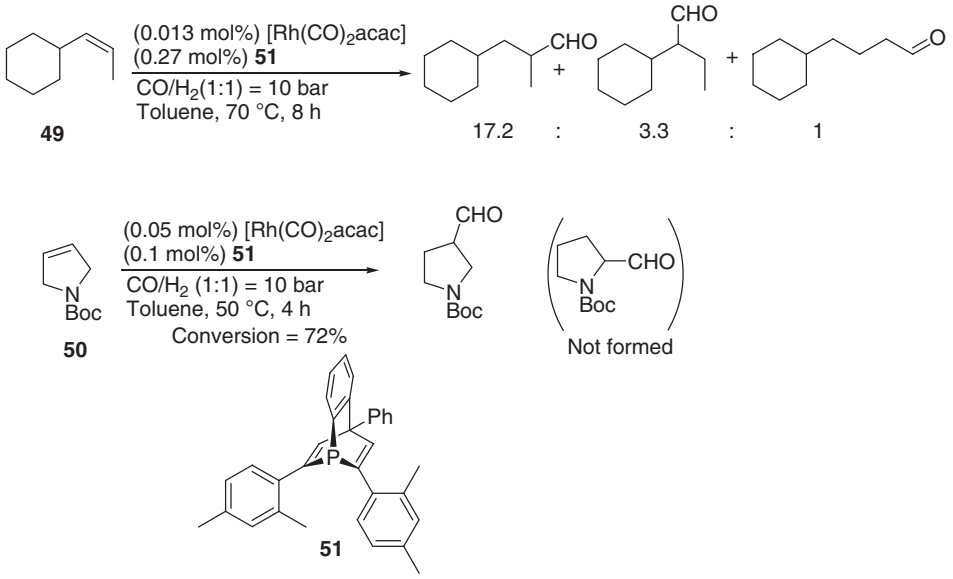
Table 7 Branched regioselective hydroformylation of 3-subsituted homoallylic alcohols **48** with directing ligand **34**



No.	*R*	*R*^{1}	*Temperature (°C)*	*Yield (%)*	*b/l*
I	H	Me	40	91	96/4
II	Me	Me	40	99	97/3
III	*n*-C_6H_{15}	Me	50	90	95/5
IV	Pr^i	Me	50	85	95/5
V	Ph	Me	40	92	99/1
VI	2-Furyl	Me	40	97	99/1
VII	CO_2Me	Me	50	99	95/5
VIII	H	*p*-CF_3-Ph	80	85	88/12
IX	Ph	Ph	50	99	86/14

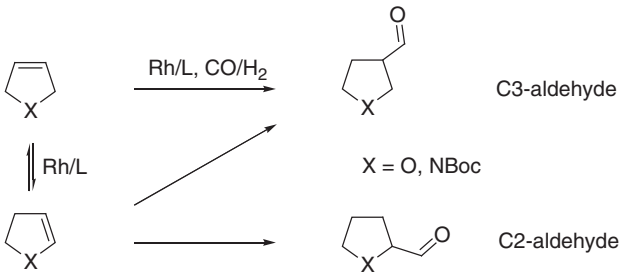
4.18.2.2.2 1,2-Disubstituted and trisubstituted alkenes

The hydroformylation of internal alkenes to selectively produce one of the branched aldehydes is a real challenge, because first, internal alkenes are less reactive and second, alkene isomerization often complicates the situation. In this regard the phosphabarrelene **51**/rhodium catalyst has turned out to be advantageous since it enables hydroformylation of internal alkenes with very high activity essentially free of alkene isomerization.[80] Two examples, the results on hydroformylation of an acyclic **49** and a cyclic **50** internal alkenic substrate, are depicted in Scheme 13.



Scheme 13 Position-selective hydroformylation of internal alkenes with a rhodium(I)/phosphabarrelene catalyst.

For the dihydropyrrole **50** (and the corresponding dihydrofuran) it is known that double-bond isomerization occurs easily, which results in the formation of a mixture of C2- and C3-aldehyde with many catalyst systems. The phosphabarrelene **51** allows suppressing this undesired isomerization while maintaining a high activity for selective 3-aldehyde formation (Scheme 14).

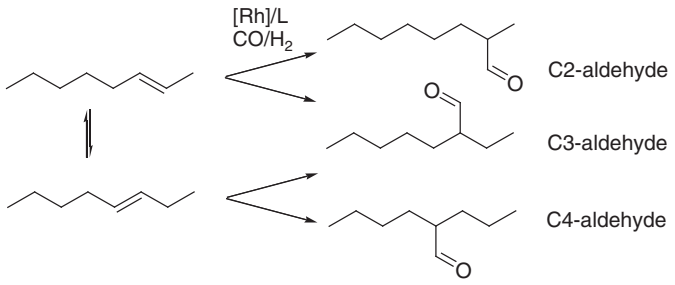


Scheme 14 Position-selective hydroformylation of heterocycloalkenes and the problem of alkene isomerization.

The regioselective hydroformylation of *trans*-2-octene is very difficult because the C2/C3 positions do neither differ in electronics nor sterics (Scheme 15). As such the phosphabarelene **51**/rhodium allowed for isomerization-free hydroformylation but regioselectivity toward the C2 aldehyde was low.[80] Conversely, the encapsulated phosphorus-based **52** rhodium catalyst provided good regioselectivity toward the C3-branched aldehyde; however, the system suffers from low reactivity (Table 8).[81]

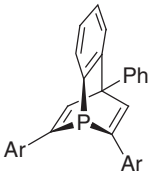
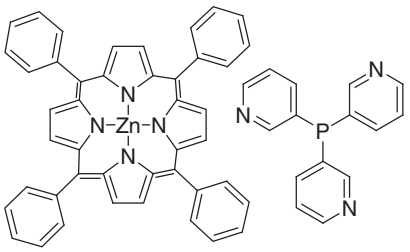
The hydroformylation of cyclic enol ethers **53–54** has been achieved using bulky phosphite **40**. Acceptable regioselectivity toward the 2-branched aldehyde on hydroformylation of 2,3-dihydrofuran **53** was observed whereas the 3,4-dihydropyran **54** gave lower regioslectivity (Scheme 16).[82]

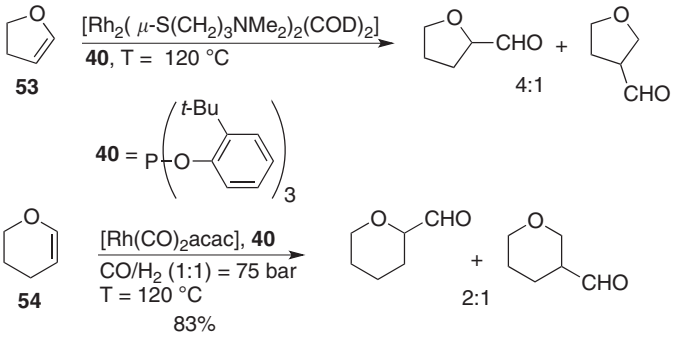
Hydroformylation of 1,2-disubstituted unsaturated esters occurred with high α-selectivity and chemoselectivity applying a rhodium/phosphaadamantane **43** catalyst. As a side reaction, hydrogenation of the alkene has been observed (Table 9).[75,76]



Scheme 15 Hydroformylation of internal olefins.

Table 8 Regioselectivity on hydroformylation of *trans*-2-octene

No.	*Ligand*	*Conditions*	*C2/C3*	*Conversion (%)*	*Isomerization (%)*
I	 Ar = 2,4-xylyl	0.014 mol%[$Rh(CO)_2$ acac], Toluene, 70 °C, 4 h, 10 bar	1.6/1	95.5	2.2
II	 **52**	0.09 mol%[$Rh(CO)_2$ acac], Toluene, 25 °C, 73 h, 20 bar	1/9	32	1.6



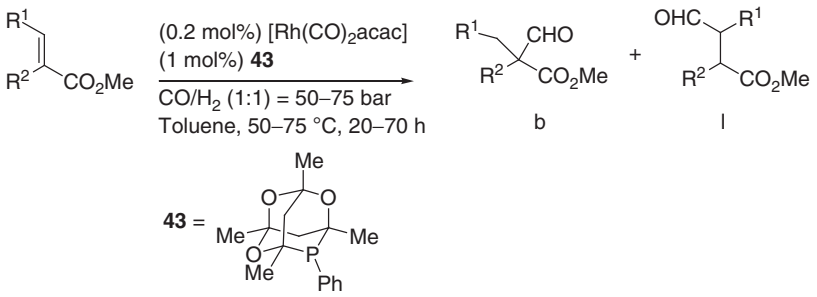
Scheme 16 Hydroformylation of 3,4-dihydropyran and 2,3-dihydrofuran.

4.18.2.2.2.1 Active substrate control

Also for 1,2-disubstituted alkenes, chelation control is an effective way to allow for unusual and high levels of regioselectivity in the course of the hydrofomylation reactions.

Hydroformylation of internal alkenes has been reported using *o*-DPPB as the directing group. Generally, high to good levels of regioselectivity in hydroformylation of allylic *o*-DPPB esters **55** have been achieved with 1,2-disubstituted alkene functions (Table 10).[70]

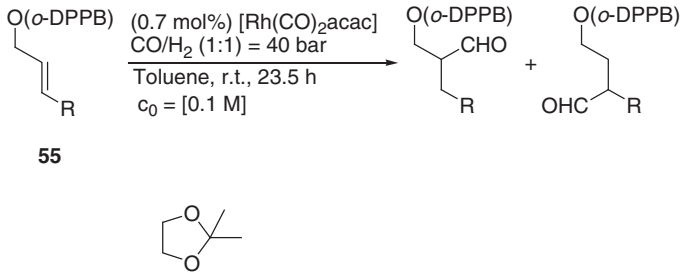
Table 9 Hydroformylation of α,β-unsaturated esters



No.	*R^1*	*R^2*	*Branched*	*Linear*	*Yield (%)*
I	Me	*n*-Pr	10	1	99
II	Ph	Me	7.5	1	70
III	Me	Me	48	1	69
IV	Me	H	>100	1	94
V[a]	Ph	H	6	1	99 (16)[a]

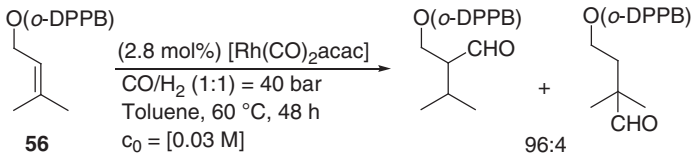
[a]99% conversion (16% alkene hydrogenation).

Table 10 Directed hydroformylation of allyl *o*-DPPB esters with disubstituted alkene functions



No.	*R*	*Conversion (%)*	*Yield (%)*	*b/l*
I	Me	>95% yield	>95%	97/3
II	*c*-Hex	>95% yield	84	81/19
III	$SiBu^tPh_2$	>95% yield	87	90/10
IV		>95% yield	94	93/7

Optimized conditions did even allow the hydroformylation of trisubstituted alkenic functions **56** (equation 13).[70]

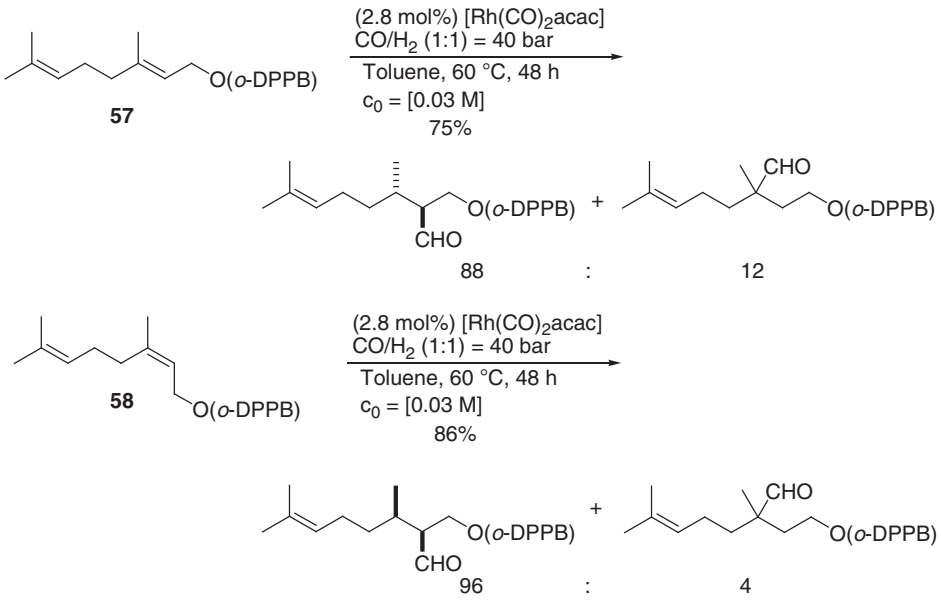


(13)

Directed hydroformylation of allyl o-DPPB esters with trisubstituted alkene function

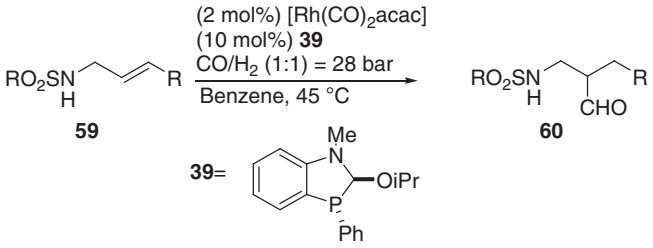
Note that in this case the regioselectivity is a result of Keulemans' rule. However, it is likely that the directing effect of *o*-DPPB group is responsible for a significant rate acceleration of the hydroformylation process in order to work under fairly mild conditions. In case this rate-accelerating effect is significant, position-selective hydroformylation of a trisubstituted alkene function in allylic position in the presence of an additional trisubstituted alkene function should be possible. Indeed, hydroformylation of geranyl **57** and neryl **58** *o*-DPPB esters occurred with high position and regioselectivity (Scheme 17).

Applying the dynamic directing ligand **39**, which operates through reversible aminal formation, a variety of allylic sulfonamides **59** has been hydroformylated to give the β-aminoaldehydes **60** selectively (Table 11).[73]



Scheme 17

Table 11 Regioselective hydroformylation of allylic sulfonamides **59** with the directing ligand **39**



No.	*R*	*Regioselectivity*	*Yield (%)*
I	Me	99/1	85
II	Cy	99/1	84
III	OTBS	94/6	83
IV	Ph	99/1	86
V	*p*-CF_3-Ph	98/2	92
VI	*p*-Cl-Ph	99/1	69
VII	*p*-MeO-Ph	97/3	87
VIII	$CH_2CH{=}CHMe$	95/5	75

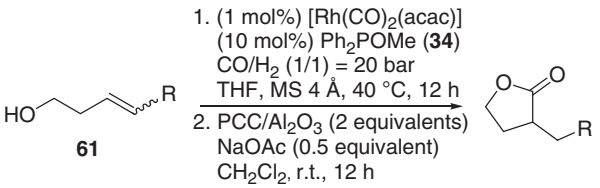
Applying diphenylphosphinite **34** as a dynamic directing group remarkable regio- and position-selective hydroformylation of homoallylic alcohols with internal olefin function **61** have been achieved (Table 12). Also here the origin of regioselectivity is the preference of a 6-*exo-trig* transition state for the hydrometallation step. Remarkable is that even a similar 1,2-disubstituted alkene function can be present without being reacted (entry 4, Table 12). Furthermore, functional groups such as a thioether or a free hydroxyl group are compatible with the reaction conditions.[72]

The reaction can be extended toward bishomoallylic alcohols **62**. In this case, the hydroxy function to which the directing group is reversibly attached and the reacting alkene function are in an unusual remote 1,4-relation. Thus, applying similar reaction conditions, with slightly increased reaction temperatures excellent regioselectivities toward the δ-lactoles were reached, which were oxidized to furnish the corresponding δ-lactones **63** (Table 13).[72]

4.18.3 Isomerizing Hydroformylation

The isomerizing hydroformylation of internal alkenes to form linear aldehydes is a reaction of immense technical importance, specifically; the transformation of the 'Raffinate-2,' a C4 feedstock derived from the steam cracker, into the corresponding

Table 12 Branched-selective directed hydroformylation of homoallylic alcohols



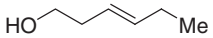
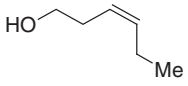
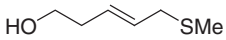
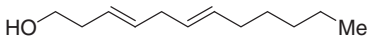
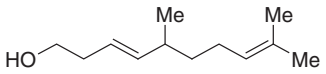
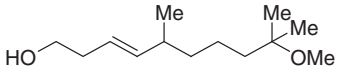
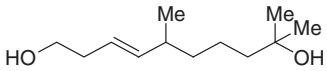
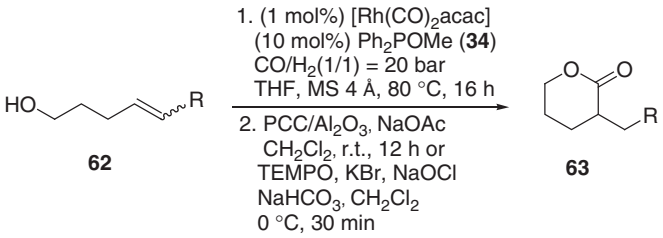
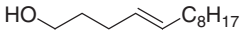
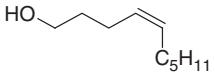
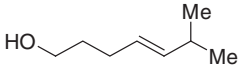
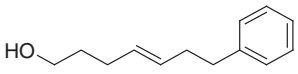
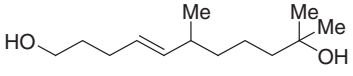
No.	*Substrate*	*Yield (%)*	*Regioselectivity*
I		85	99/1
II		88	99/1
III		84	97/3
IV		83	97/3
V		99	99/1
VI		88	99/1
VII		85	99/1

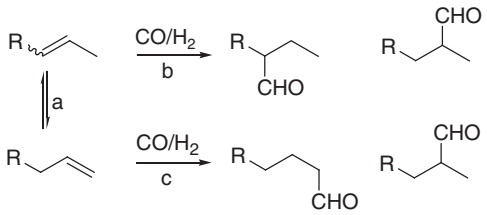
Table 13 Hydroformylation of various bishomoallylic alcohols



No.	*Substrate*	*Yield (%)*	*Regioselectivity*
I		84	99/1
II		87	99/1
III		77	99/1
IV		88	98/2
V		69	97/3

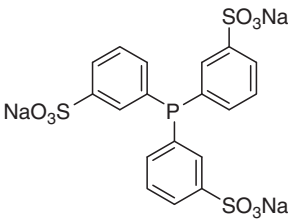
C5 aldehydes. But it could also become eventually an interesting reaction for organic synthesis since it allows for functionalization of a formally unreactive alkyl chain at its terminus through formylation (Scheme 18). Even though significant improvements have been made, still further improvements regarding chemo- and regioselectivity toward the desired linear aldehyde are needed. The basic requirements from a catalyst are, first to perform a fast isomerization from the internal to the terminal olefin which is a

delicate step since it is counter thermodynamics. Second, the hydroformylation of the terminal olefin (Scheme 18, reaction c) has to occur much faster (and with high *n* selectivity) than that of the internal olefin (Scheme 18, reaction b). This indeed should be less problematic since the reactivity of a terminal alkene is significantly higher than that for an internal one. Third, the catalyst has to possess high activity, which is measured by the turn over frequency (TOF) of the catalytic cycle. To date only a limited number of catalysts is known to fulfill these demands in part.



Scheme 18 Hydroformylation and isomerizing hydroformylation of internal alkenes.

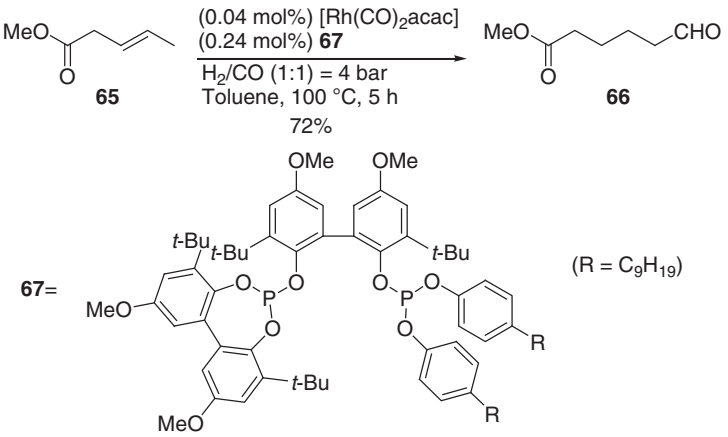
The hydroformylation of isomeric pent-2-enes in an aqueous two-phase system with a cobalt/TPPTS **64** catalyst (Figure 6) at elevated temperatures and pressures (130–190 °C, 20–100 bar) gave the desired aldehydes in good yields and linear to branched ratios of up to 70:30.[25] However, catalyst activity was low.[83]



59

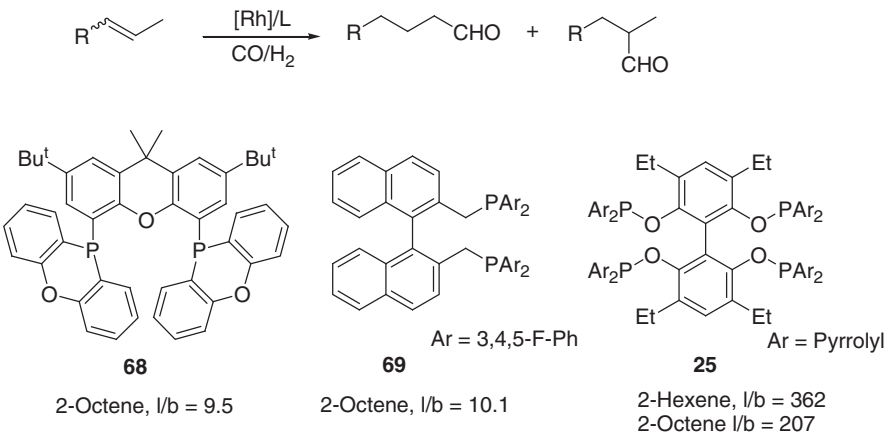
Figure 6 Structure of **64**.

A rhodium/diphosphite **67** catalyst has been applied for the isomerizing hydroformylation of methyl pent-3-enecarboxylate **65** to furnish methyl 5-formylvalerate **66** in 72% selectivity (equation 14).[84]



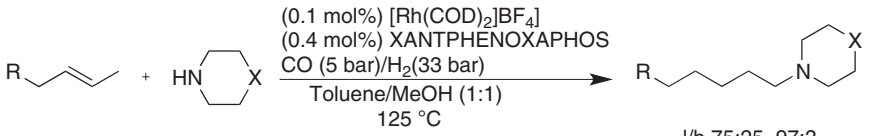
(14)

Rhodium catalysts modified with the Xantphos-type ligand **68**[85]or the electron-withdrawing Naphos-type ligands **69**[86] were efficient for the rhodium-catalyzed hydroformylation of internal long-chain alkenes to the corresponding linear aldehydes (equation 15). A high reactivity and selectivity toward the formation of *n*-nonanal was noted. The highest regioselectivities so far have been reported for rhodium catalyst modified with the pyrrole-based tetraphosphorus ligand **25** (equation 15).[87]



(15)

Furthermore, a rhodium-catalyzed hydroaminomethylation of 2-alkenes to furnish the linear amines has been realized in reasonable yields and high *n*/iso selectivity (equation 16). Mechanistically, the reaction proceeds through isomerizing hydroformylation followed by reductive amination.[88]



(16)

R = functionalized and unfunctionalized *n*-alkyl substituents
compatible functional groups: acetal, hydroxy, nitrile

Hydroaminomethylation of various internal alkenes and amines

4.18.4 Diastereoselective Hydroformylation

4.18.4.1 Introduction

The hydroformylation of alkenes is an unsymmetric addition reaction. New stereogenic centers are created by addition of *syn* gas to prochiral alkenes (enantioface differentiation) or on addition to chiral alkenes (diastereoface differentiation and/or kinetic resolution). C–H and C–C bonds are formed and in most cases simultaneous control of regiochemistry is required. The hydrometallation step is a *syn* addition and since migratory insertion of CO occurs with retention of configuration, the overall process is a stereospecific *syn* addition. Diastereoselective hydroformylation requires an energetically efficient differentiation of the diastereomorphic transition states resulting from different rates of hydrometallation of the diastereotopic alkenes faces. Such an energetic differentiation can be achieved, in general, either through substrate control or/and catalyst control. Both approaches have been used successfully to control diastereoselectivity in the course of the hydroformylation reaction.

Substrate control can be passive or active. In the first case the substrate usually possesses a reactive conformation in which one of the two diastereotopic olefin faces is spatially less accessible for the approach of the catalyst. Repulsive steric interactions control the overall process. Active substrate control relies on attractive interactions between a suitable functional group which is part of the substrate and the approaching catalyst. The result is an intramolecular catalyst trajectory leading to a cyclic transition state which, if appropriately designed, is highly ordered and may thus allow for an efficient energetic differentiation of the diastereotopic alkene faces. Furthermore, the intramolecular nature of the overall reaction often leads to a significant rate acceleration compared with a similar intermolecular process.

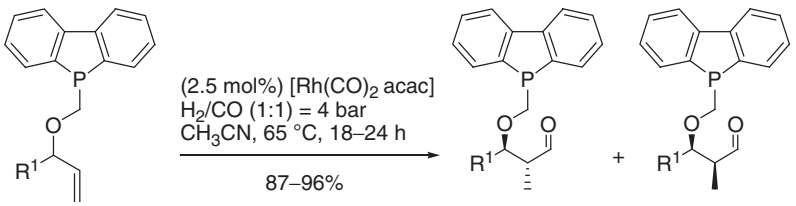
4.18.4.2 Terminal Alkenes

4.18.4.2.1 Active substrate control

The hydroformylation of allylic alcohol derivatives with a terminal alkene function is problematic since a simultaneous control of regio- and diastereoselectivity would be required. Most interesting would be a branched-selective hydroformylation since

propionate aldol-type products would be formed. *Anti*-propionate-type aldols are of significant interest since they are rather difficult to prepare using traditional aldol or allyl metal addition methodology.

Employing a dibenzophosphol-5-yl function as the catalyst-directing group which is attached as a methyl ether to allylic alcohol substrates allows a regio- and stereoselective hydroformylation to give the *anti*-aldol propionates **70** in good yields (equation 17).[89]

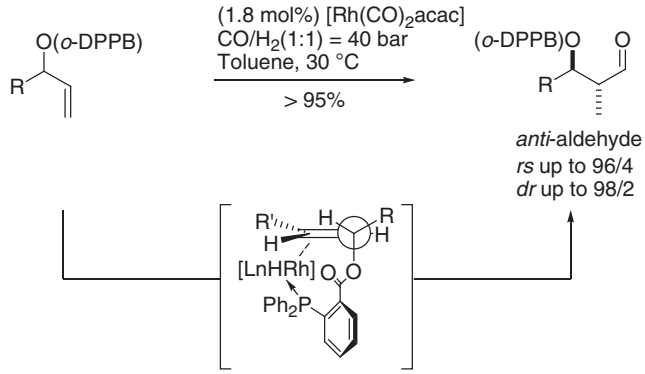


(17)

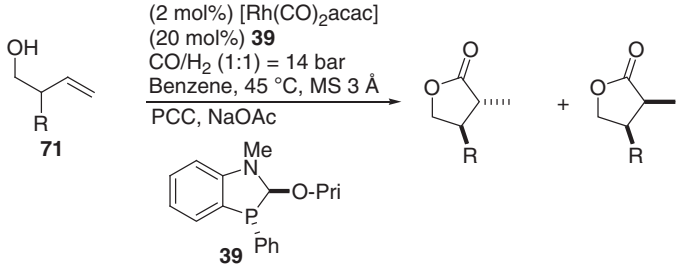
Directed hydroformylation of dibenzophosphol-5-ylmethyl ethers of allylic alcohols

Even better selectivities can be obtained when the *o*-DPPB group is employed as the catalyst-directing function (Scheme 19).[90]

Dynamic covalent directing group **39** was also efficient for the branched diastereoselective hydroformylation of 2-substituted homoallylic alcohols **71** (equation 18). The high *anti*-selectivity in the five-membered ring lactone formation can be attributed to the minimization of $A^{1,3}$ strain in the course of the selectivity-determining hydrometallation step (Table 14).[91]

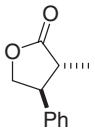
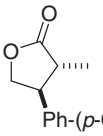
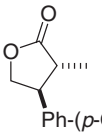
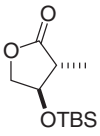
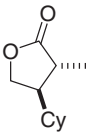


Scheme 19 *o*-DPPB-directed regio- and diastereoselective hydroformylation of allylic *o*-DPPB esters with mono- and 1,2-dialkyl-substituted alkene functions.



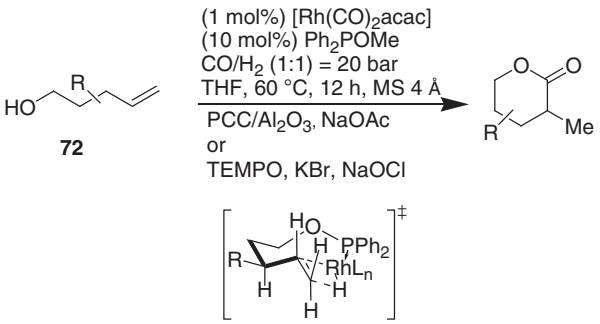
(18)

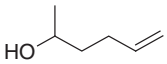
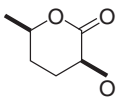
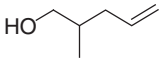
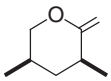
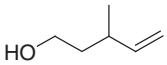
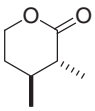
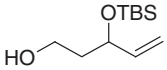
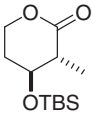
Table 14 Branched diastereoselective hydroformylation of 2-substituted homoallylic alcohols **71** with the directing ligand **39**

No.	*Product*	 Ph	 Ph-(*p*-Cl)	 Ph-(*p*-OMe)	 OTBS	 Cy
I	Yield (%)	94	98	86	75	86
II	*rr*	86/14	82/18	84/16	88/12	65/35
III	*dr*	89/11	87/13	88/12	80/20	87/13

The diastereoselectivity of the phosphinite-directed branched-regioselective hydroformylation of bishomoallylic alcohol substrates **72** with a methyl-group-bearing tertiary stereogenic center either in 1-, 2-, or 3-position, was investigated (Table 15). Although a stereogenic center in the 1- or 2-position does not result in any significant stereoinduction, in case the stereogenic center was adjacent to the alkene function, high levels of acyclic stereocontrol in favor of the *trans* diastereomer were observed. A rationale for the observed stereodiscrimination is minimization of allylic 1,3-strain in the transition state for the 7-*exo-trig* hydrometallation.[92]

Table 15 Diastereoselective branched-regioselective hydroformylation of bishomoallylic alcohols employing the dynamic directing ligand Ph_2POMe

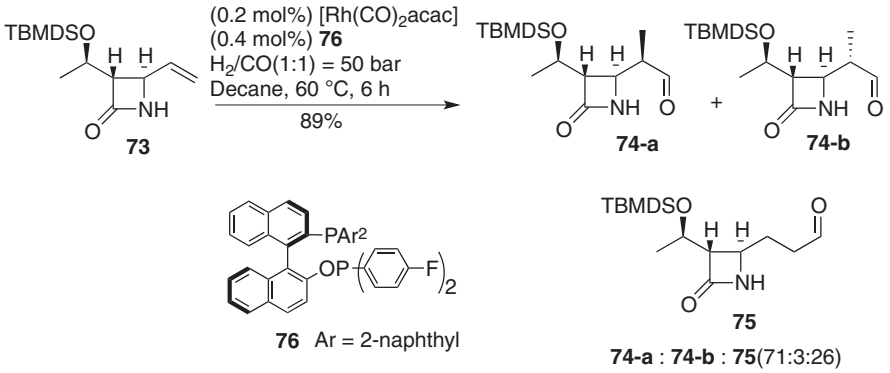


No.	*Substrate*	*Product*	*Yield (%)*	*rr*	*cis/trans*
I			99	97/3	68/32
II			78	99/1	61/39
III			82	99/1	4/96
IV			99	99/1	6/94

4.18.4.2.2 Catalyst control

In addition to pure substrate control of diastereoselectivity, employing a chiral catalyst may enforce or even overrule intrinsic substrate-direction. As chiral catalysts rhodium complexes modified with chiral-mixed phosphine/phosphite bidentate ligands based on the binaphthyl backbone have proven particularly useful.

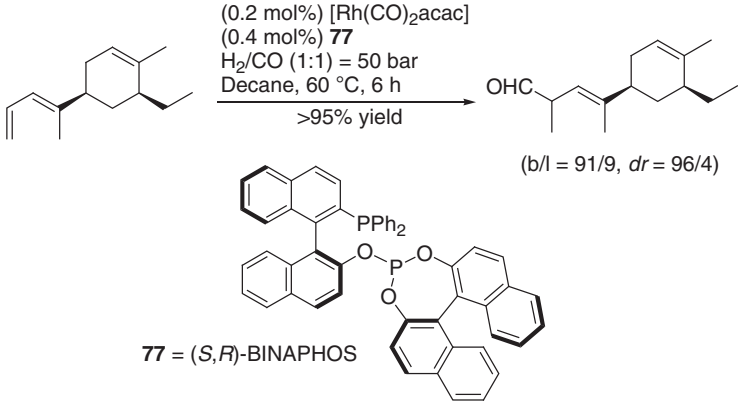
Hydroformylation of 4-vinyl-β-lactam **73** employing the rhodium/**76** catalyst gave the β-methyl branched aldehyde **74** in excellent yield as well as good regio- and diastereoselectivity (equation 19).[93] When triphenylphosphine was used as ligand, neither regio- nor diastereoselectivity were observed. Hence, diastereoselectivity is completely under catalyst control.



(19)

Regio- and diastereoselective hydroformylation of 4-vinyl β-lactam

As a similar catalyst the rhodium/(*S*,*R*)-BINAPHOS (**77**) has been used to control diastereoselectivity on hydroformylation of the chiral 1,3-diene (equation 20). Thus, α-substituted β,γ-unsaturated aldehyde was obtained in good regio- and high diastereoselectivity. This reaction was used as a key step in the course of a total synthesis of the antifungal agent ambruticin.[94]



(20)

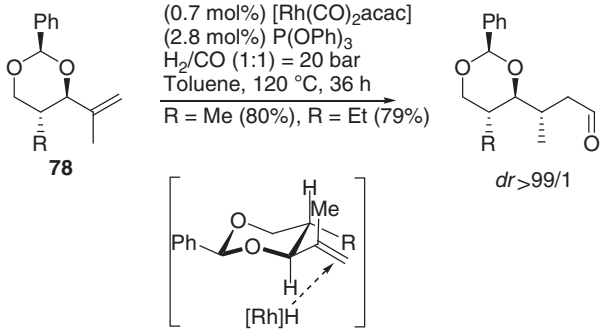
Regio- and diastereoselective hydroformylation of chiral 1,3-diene

4.18.4.3 Higher-Substituted Alkenes

4.18.4.3.1 1,1-Disubstituted alkenes

4.18.4.3.1.1 Passive substrate control

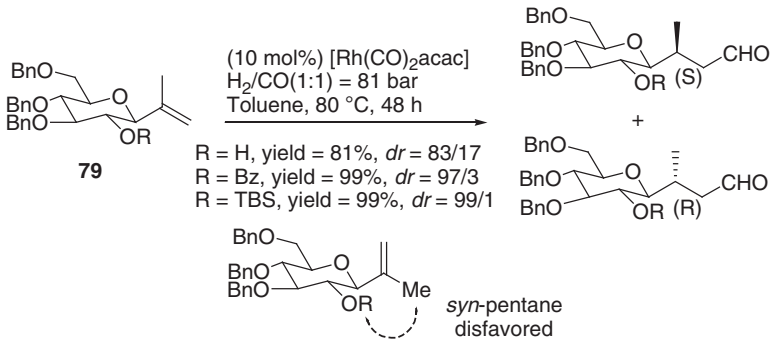
The rhodium/triphenylphosphite catalyst was applied for the hydroformylation of propenyl-substituted 1,3-dioxanes **78** and excellent diastereoeselectivity was obtained. The *anti*-configured substituent R was essential for good levels of stereoinduction since it induces a reactive alkene conformation in which the 'unlike' diastereotopic face is blocked through the R-substituent (equation 21).[95]



(21)

Diastereoselective hydroformylation of 2-propenyl substituted 1,3-dioxanes

The hydroformylation of 1,1-disubstituted C-glycosylated alkenes **79** occurs with high levels of diastereoselectivity to give (*S*)-aldehydes preferentially. Using bulky protecting groups R for the C2-hydroxyl resulted with higher selectivities (equation 22).[96] A preferred substrate conformation which minimizes *syn*-pentane interaction as well as $A^{1,3}$ strain may account for the observed diastereoselectivity.

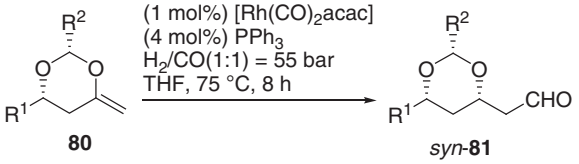


(22)

Diastereoselective hydroformylation of 1,1-disubstituted C-glycosylated alkenes **79**

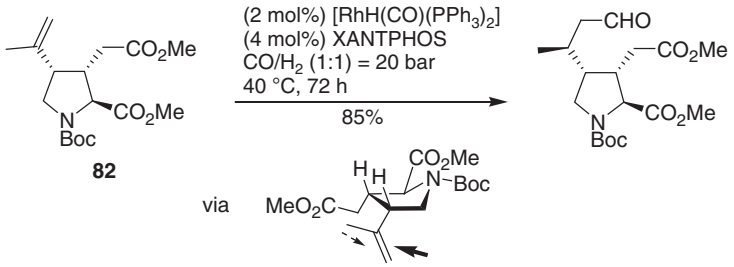
Rhodium-catalyzed hydroformylation of substituted 4-methylene-1,3-dioxanes **80** with the rhodium/triphenylphosphine catalyst proceeds with good regioselectivity and in high diastereoselectivity (>50/1) to give the acetal protected *syn*-3,5-dihydroxyaldehydes **81** as the exclusive product (**Table 16**).[97]

Table 16 Diastereoselective hydroformylation of 4-methylene-1,3-dioxanes



No.	R^1	R^2	*Yield (%)*	*dr*
I	H	Bu^t	81	12/1
II	Me	Bu^t	72	13/1
III	Me	Me	75	13/1

A recent example is the highly diastereoselective hydroformylation of a kainic acid derivative **82** (equation 23).[98] The selective formation of the major diastereomer has been explained via a reactive substrate conformation in which allylic 1,2-strain has been minimized. In this situation the *cis*-positioned methylene carbonylmethoxy group controls the catalyst attack to occur from the si-face exclusively.



(23)

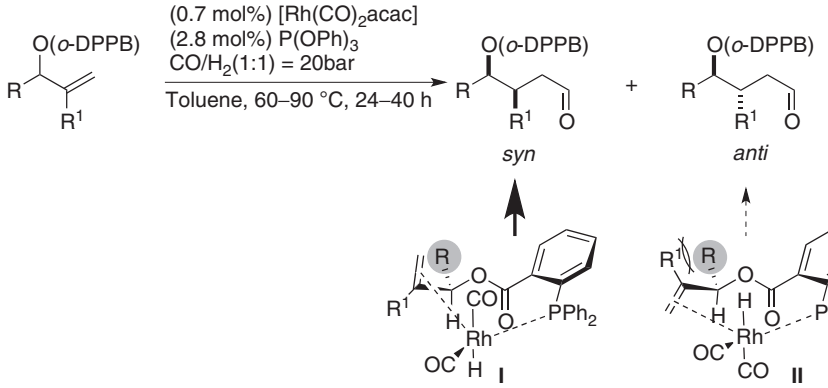
Diastereoselective hydroformylation of a kainic acid derivative relying on passive substrate control

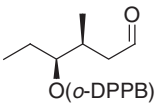
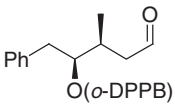
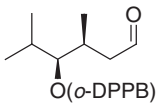
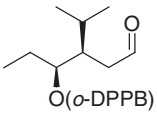
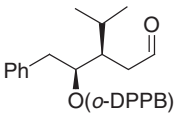
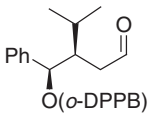
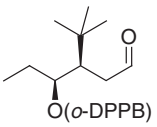
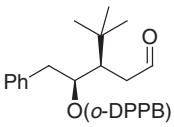
4.18.4.3.1.2 Active substrate control

Diastereoselective hydroformylation of 1,1-disubstituted alkenyl and allyl carbinols has been reported using *o*-DPPB as the directing group.[99] The linear aldehyde should be exclusively obtained as a result of Keuleman's rule. Hence, the only selectivity issue that remains to be controlled is that of diastereoselectivity. Hydroformylation of *o*-DPPB esters proceeded with high levels of

acyclic stereocontrol to furnish the *syn*-aldehydes as the major diastereomers (Table 17).[100] In further studies it was observed that diastereoselectivity is a function of the steric demand of both, the substituent at the controlling stereocenter R, and the substituent at the 2-position of the allylic alcohol system R^1. Increasing the size of both, increases diastereoselectivity (Table 17).[28] To rationalize the experimentally observed diastereoselectivities, the starting diastereomeric alkene complexes **I** and **II** should serve as good models for the corresponding competing diastereomorphic transition states for hydrometallation. A repulsive interaction between substituents R^1 and R favors the pathway via intermediate complex **I** ($A^{1,2}$ strain minimized) to give the *syn*-diastereomer as the major product.

Table 17 Diastereoselective hydroformylation of methallylic *o*-DPPB esters

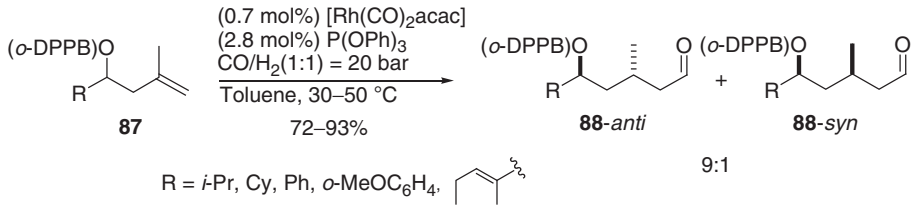


No.	Product	dr	Product	dr	Product	dr
I		60/40		72/28		96/4
II		82/18		92/8		991
III		94/6		99/1		

The methodology has been applied for the construction of *syn–syn* and *anti-syn* stereotriads **83**, **84**, and **85** which are major building blocks for polypropionate synthesis (Scheme 20).[101] High levels of diastereoselectivity were obtained irrespective of the relative configuration (*syn* or *anti*) in the substrate.

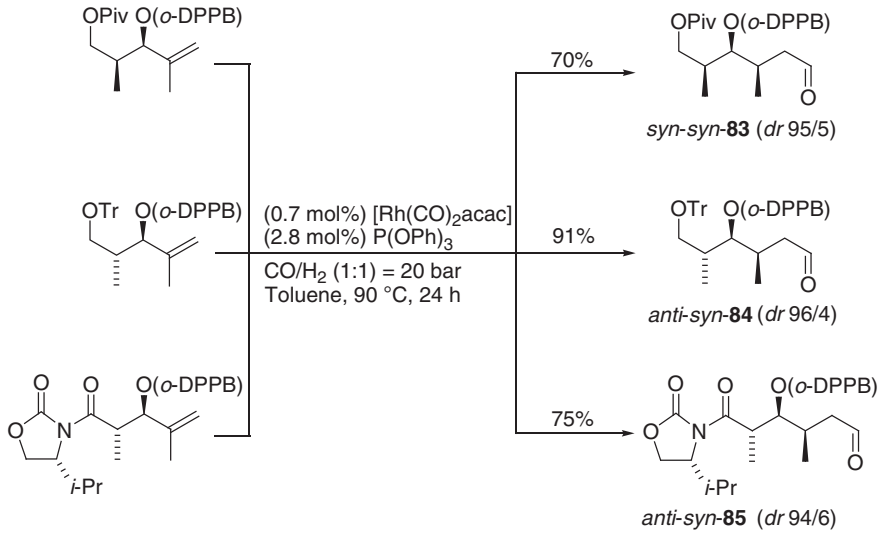
This methodology has been successfully used for the synthesis of the complex alkaloid ((+)-Clavolonine) **86** (Scheme 21). Here the directing *o*-DPPB group has been applied to control the diastereoselectivity in two subsequent hydroformylation steps. Although in step one a remarkable chemo-, regio-, and diastereoselectivie hydroformylation of the 1,1-disubstituted alkene function in the presence of a trisubstituted alkene and alkylchloride function was achieved, the hydroformylation of exocyclic methylene cyclohexene proceeded highly diastereoselective via transition state **I**.[102] Hence, directed hydroformylation is now a well-developed methodology suited for application in total synthesis.

Interestingly, not only 1,2- but also 1,3-asymmetric induction can be effected employing the catalyst-directing *o*-DPPB group. Thus, hydroformylation of homomethallylic *o*-DPPB esters **87** (equation 24) furnishes the *anti*-aldehydes **88** in good yields and diastereoselectivities.[103]

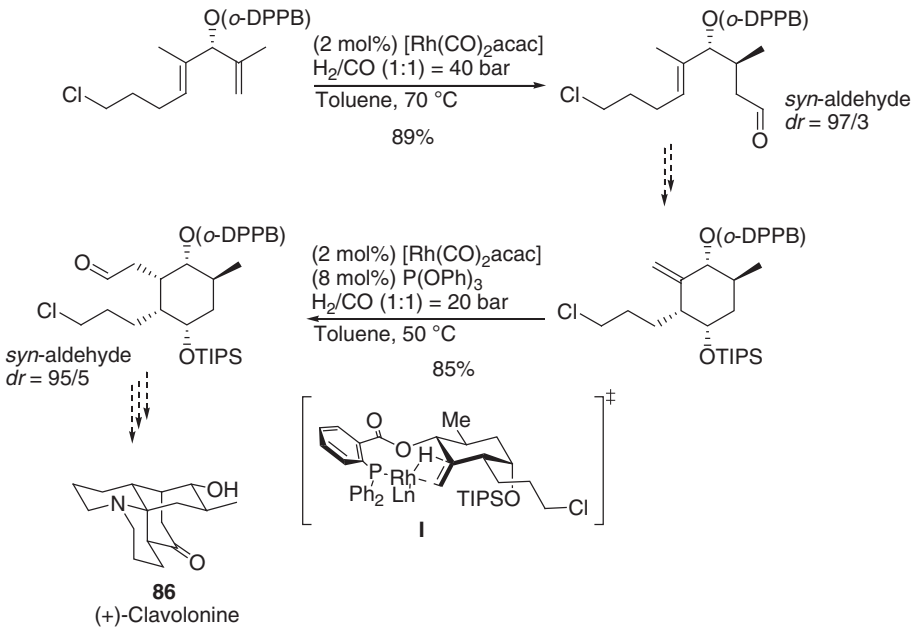


(24)

Directed diastereoselective hydroformylation of homomethallylic *o*-DPPB esters



Scheme 20 Stereotriad construction employing the *o*-DPPB-directed diastereoselective hydroformylation.



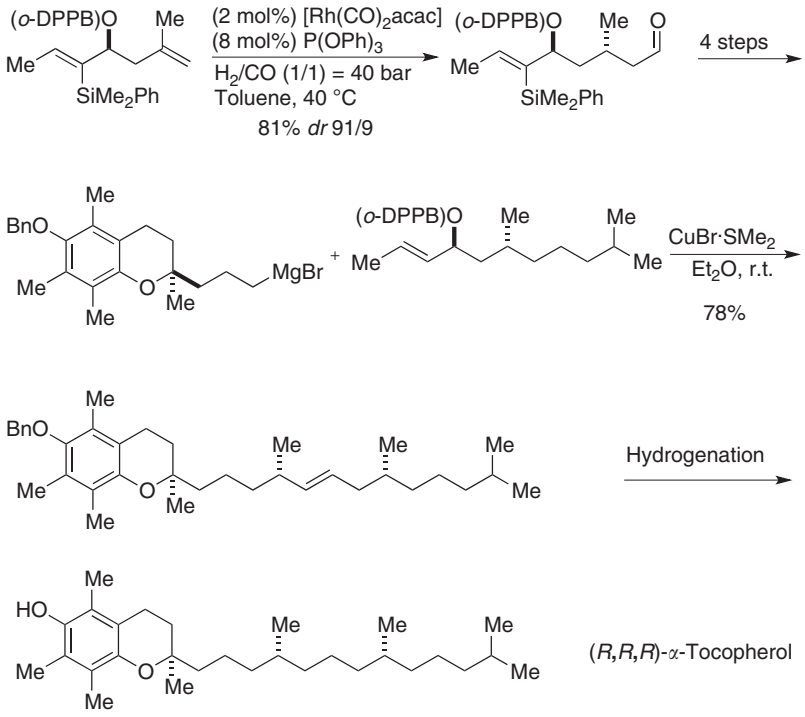
Scheme 21

This strategy has been successfully used for the synthesis of the natural product α-tocopherol, which is the most active member of vitamin E compounds (Scheme 22).[104] The reagent-directing group (*o*-DPPB) served to control the diastereoselectivity during the course of the rhodium-catalyzed hydroformylation of the homomethallylic precursor. The *anti*-aldehyde was obtained in 81% yield as a 91/9 mixture of diastereomers which were separated after a reduction step.

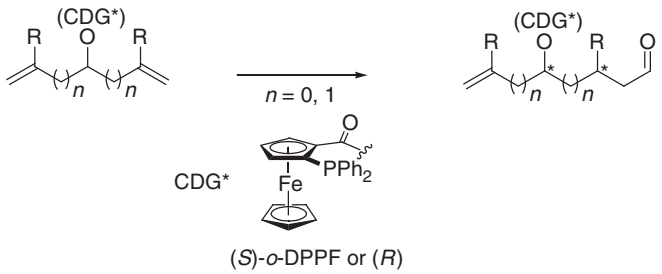
4.18.4.3.1.3 Directed desymmetrizing hydroformylation

In all previous cases stereochemical information for directed diastereoselective hydroformylation was provided by the substrate. However, with prochiral substrates the chiral information has to reside in the catalyst-directing group. The *ortho*-diphenylphosphanyl ferrocene carboxylate system (*o*-DPPF) was used as a planar chiral variant of the achiral *o*-DPPB group for the hydroformylation of symmetrical dialkenylcarbinols ($n=0$) and diallylcarbinols ($n=1$) (Scheme 23). Removal of the substrate-bound catalyst-directing *o*-DPPF group can be achieved through saponification after protection of the aldehydes such as dimethylacetals.

Interestingly, a stereoselective monohydroformylation could set two stereogenic centers simultaneously to give potentially interesting chiral building blocks for polyketide synthesis. However, stereoselective hydroformylation of these substrates is



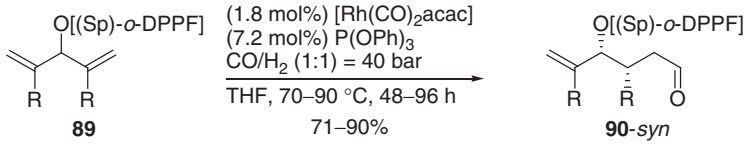
Scheme 22



Scheme 23

particularly challenging since diastereotopic alkene group discrimination and diastereotopic alkene face discrimination have to be managed simultaneously.

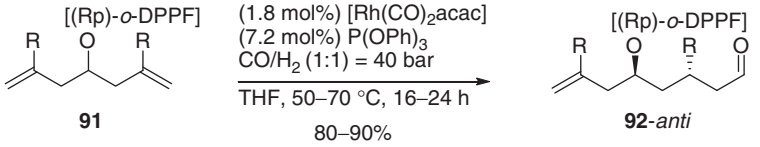
The hydroformylation of dialkenylcarbinol *o*-DPPF esters **89** occurs with good diastereotopic face discrimination and perfect diastereotopic group discrimination to furnish in enantiomerically pure form the *syn*-aldehydes **90** as the major product in good yields and high diatereoselectivities (equation 25).[105] Diastereotopic face discrimination increases with the size of the R-substituent at the alkene.



(25)

Desymmetrizing hydroformylation of dialkenyl carbinol *o*-DPPF esters

Diallyl carbinol-*o*-DPPF esters **91** are further excellent substrates for the desymmetrizing *o*-DPPF-directed hydroformylation. The *anti*-aldehydes **92** were obtained in good yield, excellent diastereoselectivity, and in enantiomerically pure form (equation 26).[106]



(26)

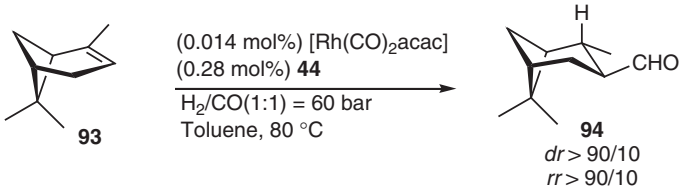
R = Me, Et, Pr^i, Ph, CH_2OTBS *dr* 87/13 to 96/4

Desymmetrizing hydroformylation of diallylcarbinol *o*-DPPF-esters

4.18.4.3.2 Internal alkenes

4.18.4.3.2.1 Passive substrate control

A difficult challenge is the hydroformylation of α-pinene since the trisubstituted alkene is rather reluctant toward hydroformylation. However, employing a phosphinine 44-modified rhodium catalyst hydroformylation of α-pinene **93** occurred smoothly to yield aldehyde **94** (73% conversion) in good chemo-, regio-, and diastereoselectivity (equation 27).[107]

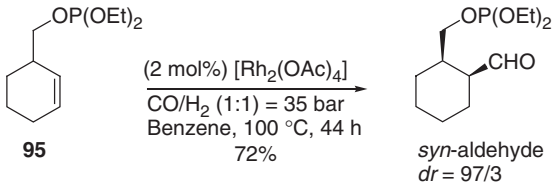


(27)

Stereoselective hydroformylation of (–)-α-pinene

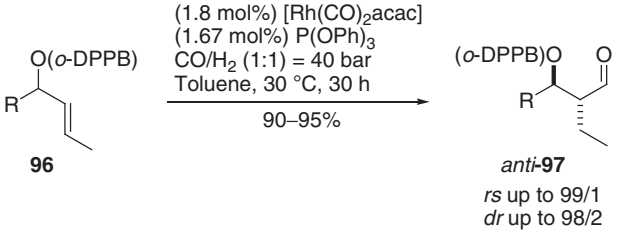
4.18.4.3.2.2 Active substrate control

An early example is the chelation-controlled hydroformylation of cyclohexenyl phosphite **95** which provided a single regioisomer in good yield and excellent diastereoselectivity (equation 28).[108]



(28)

Allylic alcohols with a 1,2-*trans*-disubstituted alkene function **96** could be hydroformylated to give in good regio- and diastereoselectivities formal *anti*-aldols products **97** (equation 29). Minimization of $A^{1,3}$ strain in the course of the selectivity-determining hydrometallation step accounts for the observed diastereoselectivity.[90]

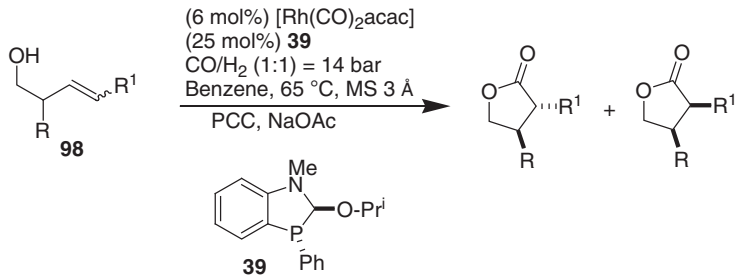


(29)

When applying the dynamic directing ligand **39**, high regio- and diastereoselectivity were noted for the hydroformylation of 2-substituted homoallylic alcohols with internal double bonds **98** (Table 18).[92]

The dynamic directing phosphinite ligand was used for the regio- and diastereoselective hydroformylation of 2,5-cyclohexadienyl-1-carbinols **99**. Only one of the two alkene functions was functionalized through hydroformylation to form an attractive quaternary carbon center leaving the second alkene function for potential further functionalization (Table 19). The *syn*-bicyclic lactones **100** were obtained as single diastereomers after PCC oxidation of the corresponding *syn*-lactols without epimerization.[109]

Table 18 Diastereoselective hydroformylation of homoallylic alcohols **98** with the directing ligand **39**



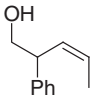
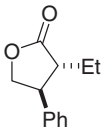
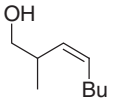
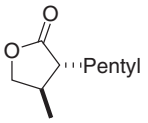
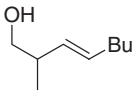
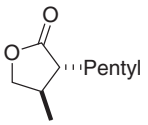
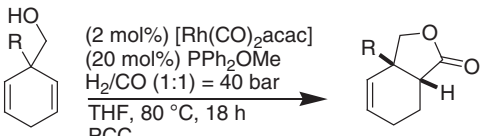
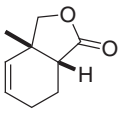
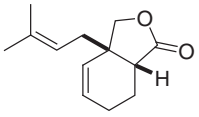
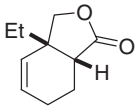
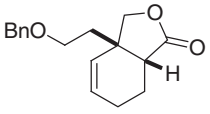
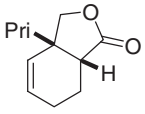
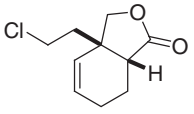
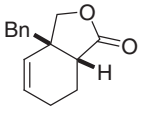
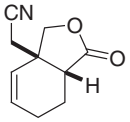
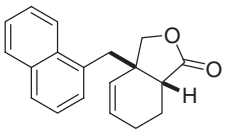
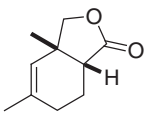
No.	*Substrate*	*Product*	*Yield (%)*	*rr*	*dr*
I			88	98/2	98/2
II			70	95/5	92/8
III			69	94/6	78/22

Table 19 Regio- and diastereoselective hydroformylation of 2,5-cyclohexadienyl-1-carbinols employing the directing ligand PPh_2OMe



No.	*Product*	*Yield (%)*	*Product*	*Yield (%)*
I		80		79
II		87		83
III		30		66
IV		79		80
V		66		92

4.18.5 Enantioselective Hydroformylation

4.18.5.1 Introduction

Asymmetric hydroformylation is of high potential value for organic synthesis since it provides direct access to a variety of enantiomerically enriched aldehydes from inexpensive feedstock (alkenes and syngas). Even though asymmetric hydroformylation has been studied extensively, however, success is still limited due to several technical challenges. Among the most significant issues are (1) the low reaction rates at low temperature where good selectivities are usually observed, (2) the difficulty to control simultaneously the regio- and the enantioselectivity, and (3) the limited substrate scope for any single ligand. It was also observed that traditional chiral ligands which are successful in hydrogenation reactions, in general, completely fail to induce asymmetry in the course of the hydroformylation. For this reason special ligand classes were developed for hydroformylation which are based either on mixed phosphine/phosphite systems, diphosphites, or more recently phospholanes **105** and **106**. Figure 7 gives a selection of the most useful ligands for enantioselective hydroformylation.

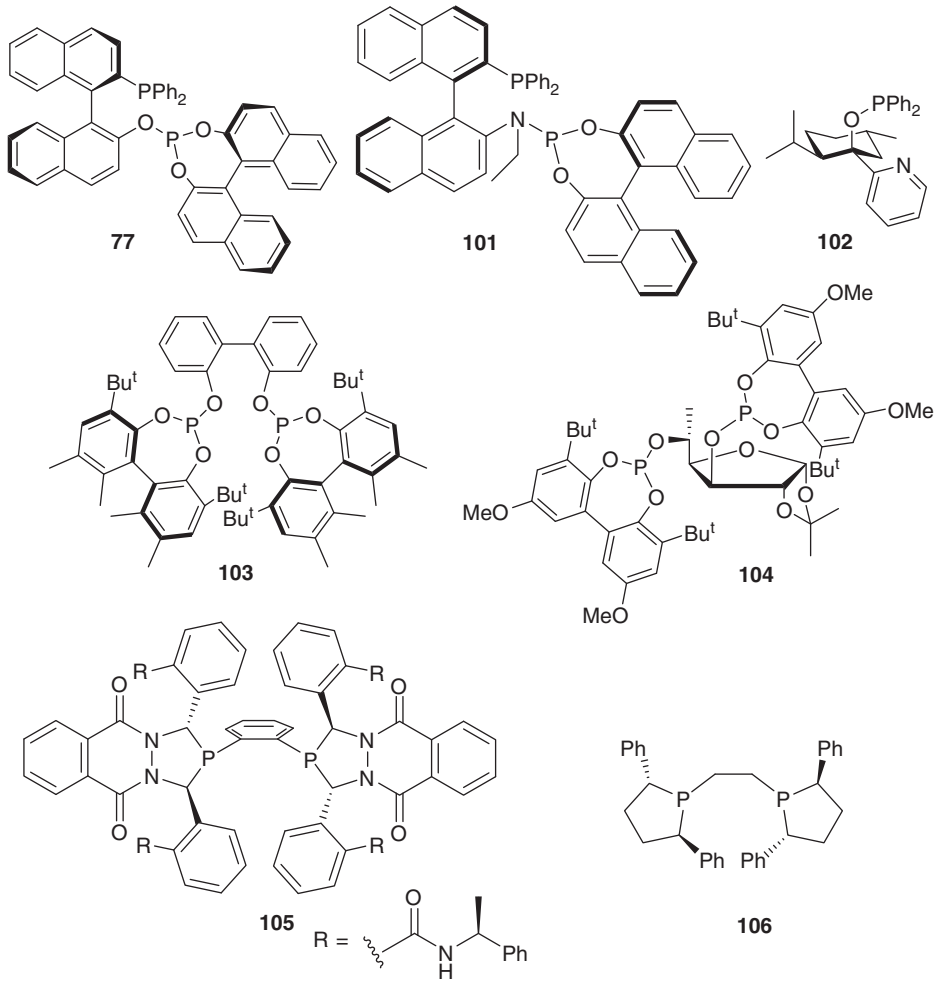
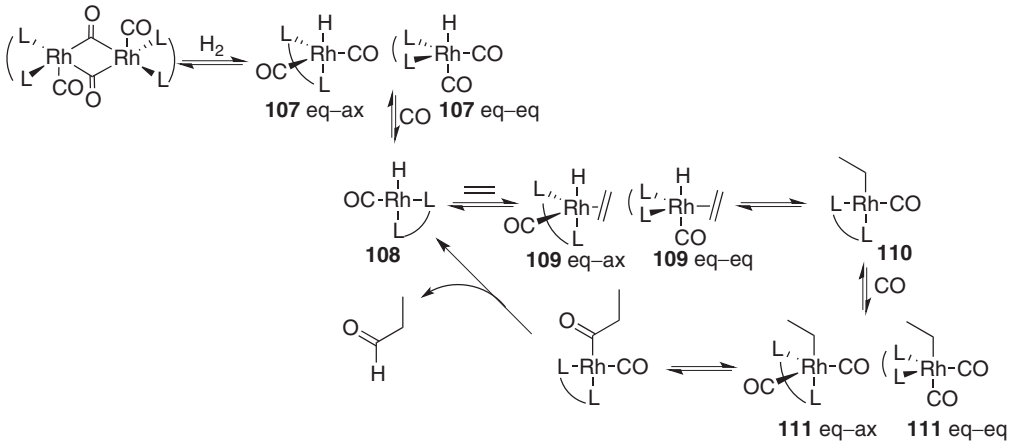


Figure 7 Chiral ligands for enantioselective hydroformylation.

4.18.5.2 Mechanism

The well-established mechanism of the Rh-catalyzed hydroformylation is described for bidentate ligands in Scheme 24.[110] Mechanistic insight into asymmetric hydroformylation employing chelating chiral ligands have been gained through structural characterization of the catalyst resting state as well as by *in situ* spectroscopic techniques (HP-IR and HP-NMR).[25] For bidentate ligands (L–L), the common starting complex is the [RhH(L–L)$(CO)_2$] species **107** containing the ligand coordinated in equatorial positions (**107** eq–eq) or in an axial–equatorial configuration (**107** eq–ax). During catalysis complex **107** has been identified as the resting state of the catalyst.

Dissociation of equatorial CO from **107** leads to the square-planar intermediate **108**, which associates with alkenes to give complexes **109**, where the ligand can again be coordinated in two isomeric forms eq–ax and eq–eq, having a hydride



Scheme 24

in an apical position and the alkene coordinated in the equatorial plane. Experimental observations showed that high enantioselectivity in asymmetric hydroformylation of alkenes is obtained using ligands that lead to the formation of only one isomer of the resting state **107**. The coexistence of the two possible isomers in solution was shown to always provide lower enantioselectivity.

4.18.5.3 Terminal Alkenes

The enantioselective hydroformylation of monosubstituted alkenes (Table 20) was extensively studied due to the interest of the synthesis of 2-substituted branched aldehydes using chiral hydroformylation catalysts.[111] So most studies have been limited to terminal alkenes which display intrinsic high regioselectivities toward the chiral-branched regiosisomer due to electronic effects or the use of chelating substituents. Typical substrates which can now be hydroformylated with excellent *ee*'s are vinylarenes, vinyl acetate, and allyl cyanide. In particular, diphosphite, phosphine–phosphite, and bisphosphacyclic ligands provided the best results for this class of substrates (Table 20).[25]

Table 20 Branched-selective hydroformylation of 2-functionalized terminal alkenes

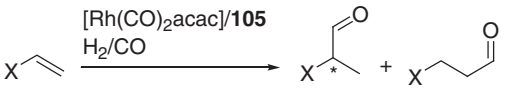
No.	*L*	*R* = *Ph*		*R* = *CH*$_2$*CN*		*R* = *OAc*		*References*
I		*Regio (%)*	*ee (%)*	*Regio (%)*	*ee (%)*	*Regio (%)*	*ee (%)*	
II	104	99	93			99	73	112
III	77	90	94	72	66	86	92	113
IV	101	89	99			93	96	114
V	105	97	89	83	87	98	96	115
VI	106	98	94	88	87	99	82	116

For enantioselective hydroformylation of acrylates the P,N-mixed ligand **102** has been reported to furnish the best selectivities.[104] Diazaphospholane **105** enables an efficient enantioselective hydroformylation of vinylcarboxamides under mild conditions (Table 21).[117] The same ligand was also used for the asymmetric hydroformylation of dialkylacrylamides with moderate to good enantioselectivities. However, the system suffers from low reactivity (Table 21).[117]

Allylic alkenes are particularly challenging substrates for the hydroformylation reaction. In most cases, the linear aldehydes are obtained as the major isomers. For example, the asymmetric hydroformylation of allyl alcohols **112** using the phosphine –phosphite ligand **77** yields a 1/9 ratio of branched to linear aldehyde with only 16% *ee*.[118] With diazaphospholane ligand **105**, the same reaction proceeds with excellent enantioselectivity, although the regioselectivity still favors the linear aldehyde. However, analogous allyl ethers react with much higher levels of selectivity and excellent enantioselectivities (Table 22).[117b]

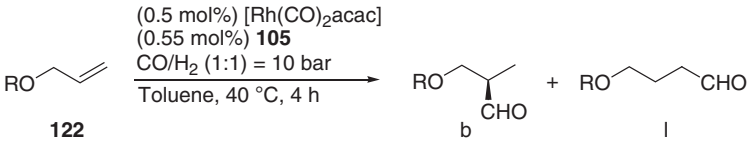
The Rh/(*S*,*R*)-**101** catalyst was successfully used for the enantioselective hydroformylation of *N*-allylamides, *N*-allylcarbamates, and *N*-allysulfonamides **113**.[119] Indeed, excellent enantioselectivities and good regioselectivites in favor of the branched isomer were obtained (Table 23).

Table 21 Enantioselective hydroformylation of functionalized alkenes



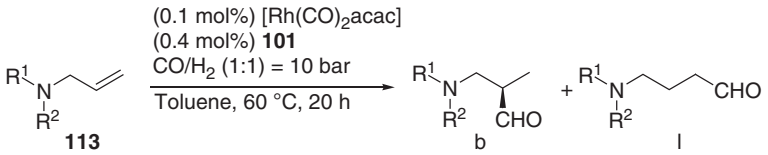
No.	*X*	*b/l*	*ee (%)*
I	NHC(O)OBn	51/1	94
II	NHC(O)Bu^t	33/1	99
III	NHC(O)CF_3	50/1	99
IV	NHC(O)Me	27/1	86
V	NPht	50/1	95
VI	C(O)NEt_2	30/1	82
VII	C(O)NPr^i_2	56/1	74
VIII	C(O)NMe(OMe)	56/1	71

Table 22 Asymmetric hydroformylation of allylic alcohols



No.	*R*	*Conversion (%)*	*b/l*	*ee (%)*
I	H	99	1/3.4	95
II	TMS	99	2/1	97
III	TBS	99	2/1	96
IV	Ph	99	2.6/1	96

Table 23 Asymmetric hydroformylation of *N*-allylamides

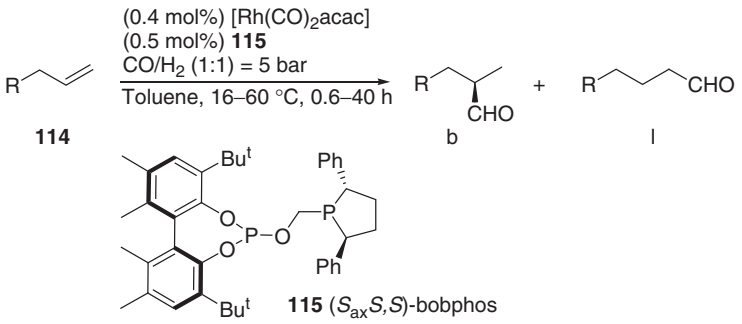


No.	*R^1*	*R^2*	*Conversion (%)*	*b/l*	*ee (%)*
I	Boc	H	99	1.9/1	94
II	Bz	H	99	3.5/1	95
III	Ts	H	99	2/1	94
IV	*p*-NO_2PhSO_2	H	99	2.5/1	92
V	*p*-MeOPhSO_2	H	99	2.4/1	96
VI	Ts	Me	99	2/1	94
VII	Phthaloyl		99	5.2/1	96
VIII	Boc	Boc	99	2.5/1	99

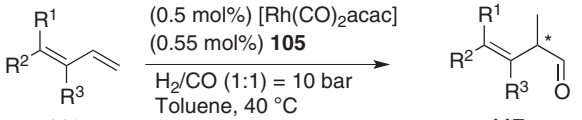
The enantioselective hydroformylation of linear alkyl-substituted olefins **114** is problematic since regioselectivity toward the branched aldehyde is, in general, lacking. However, a new phosphine–phosphite ligand **115** has recently been discovered which gives unexpectedly high levels of regioselecitiviy in combination with good levels of enantioinduction (Table 24).[120]

High levels of regio- and enantioselectivity are obtained in the hydroformylation of conjugated dienes **116** using chiral bisdiazaphospholane ligand **105** to give β,γ-unsaturated aldehydes **117** that retain a double bond for further functionalizations (equation 30).[121]

Table 24 Hydroformylation of alkenes of type $RCH_2CH=CH_2$ using Rh/bobphos catalyst



R	*Yield (%)*	*b/l*	*ee (%)*
Ph	90	4/1	90
C_6F_5	81	6.2/1	91
p-Bu^{t}Ph	99	3/1	92
CH_2Ph	89	2.5/1	75
C_3H_7	70	3/1	93
CN	99	10/1	81
C(O)NPhMe	71	4.5/1	92



(30)

R^1 = H, Me
R^2 = Aryl, Hetaryl, OAc, OMe, OTIPS, CO_2Et
R^3 = H, Me

rr = 88–99%
ee = 90–97%
10 examples

Enantioselective hydroformylation of conjugated dienes

4.18.5.4 Higher-Substituted Alkenes

4.18.5.4.1 1,1-Disubstituted alkenes

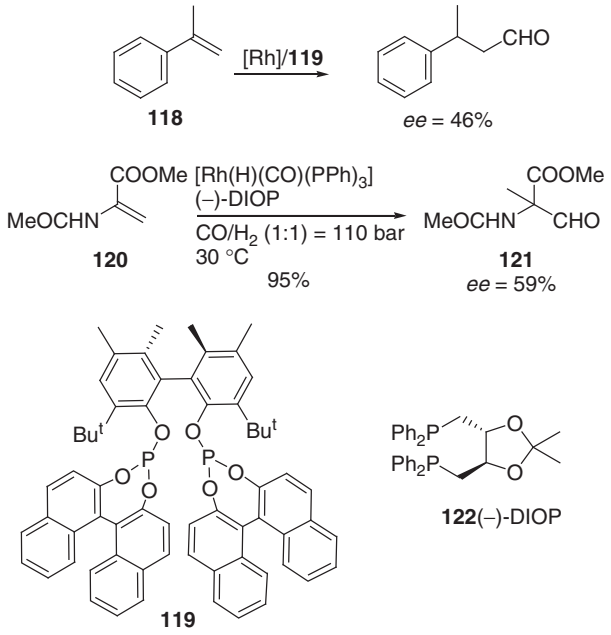
The Rh-catalyzed asymmetric hydroformylation of α-methylstyrene **118** using diphosphite ligand **119** (Scheme 25) to form the linear product was recently patented. The enantioselectivity was, however, moderate (*ee* up to 46%).[122] Interestingly, when the hydroformylation of amido acrylate **120** (Scheme 25) was carried out applying an (*R*,*R*)-DIOP **122**-modified rhodium catalyst, the branched product **121** containing a quaternary stereogenic center was exclusively obtained in high yield but in moderate enantioselectivity (*ee*'s up to 59%).

Effective rhodium-catalyzed enantioselective hydroformylation of functionalized 1,1-disubstituted alkenes (α-alkylacrylates **123**) under mild conditions was achieved using the P-chirogenic ligand BenzP* **125** (Table 25). This methodology furnishes an efficient access to interesting 1,4-dicarbonyl **124** building blocks with an alpha-tertiary stereogenic center in good yields, excellent regioselectiviy, and good levels of enantioselectivity.[123]

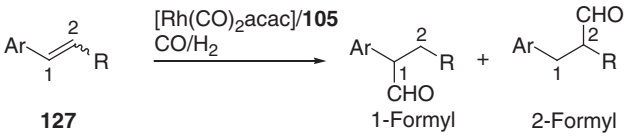
4.18.5.4.2 Internal alkenes

For symmetrical 1,2-disubstituted alkenes **126** the problem of regioselectivity is omitted. The best results to date were obtained applying the BINAPHOS ligand **77** (Table 26).[124] Interestingly, it was found that *E*-alkenes gave significantly lower enantioselectivites than their *Z*-counterparts.

The asymmetric Rh-catalyzed hydroformylation of *trans*-anethole using the BINAPHOS ligand proceeded with excellent regioselectivity (98%) and a remarkable *ee* (80%) giving the 1-formyl product.[124] Recently, bisdiazaphospholane ligand **105** was used for the asymmetric hydroformylation of internal aryl alkenes **127** (equation 31). The 1-formyl products were obtained in good regio- and enantioselectivities. However, the system suffers from low reactivity (conversion from 6% to 67%, TON = 65–350).[125]



Scheme 25 Asymmetric hydroformylation of 1,1-disubstituted alkenes.



(31)

No	R = Ph, Ar = Ph		R = Me, Ar = Ph *cis* alkene		R = Me, Ar = Ph *trans* alkene	
I	*rr*	*ee* (%)	1-Formyl/2-formyl	*ee* (%)	1-Formyl/2-formyl	*ee* (%)
II	–		11	92	20	67

Asymmetric hydroformylation of internal aryl alkenes

Bisdiazaphospholane ligand **105** was also applied for the asymmetric hydroformylation of internal enamides, a *Z*-crotyl silylether and cinnamyl alcohol. Indeed, good regioselectivities and enantioselectivities were noted (Table 27).[117]

This ligand **105** was efficiently used during a synthesis of the macrocyclic lactone natural product (+)-Patulolide C (Scheme 26).[126]

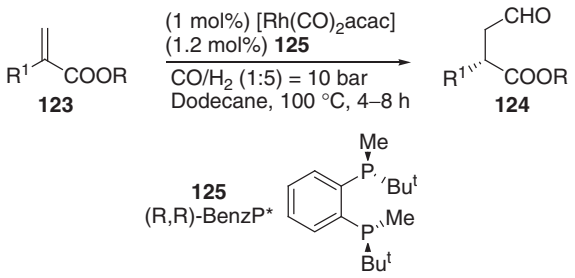
Recently, a conceptually new strategy has been applied for asymmetric catalysis. Thus, a dynamic chiral catalytic directing group **130** was designed which allowed for simultaneous control of regioselectivity and enantioselectivity in the course of the hydroformylation of allylic amines **128**. The primary *β*-aminoaldehydes were directly reduced to furnish the corresponding 1,3-aminoalcohols **129** in moderate to good yields, regioselectivity, and enantioselectivity up to 92% (Table 28).[127]

4.18.5.4.2.1 Cyclic substrates

Among monocyclic 1,2-disubstituted alkene substrates, five-membered ring heterocycles such as dihydrofurans and dihydropyrroles **131** have been studied most. With these substrates, the simultaneous control of the chemo-, regio-, and enantioselectivity is a key issue, since the presence of a heteroatom can facilitate olefin isomerization in the presence of a metal-hydride species. This isomerization process is of critical importance since it has a direct influence not only on the regioselectivity of the reaction but also on the enantioselectivity since the opposite enantiomers of tetrahydro-3-carbaldehyde are formed from the allylic **131a** and vinylic **131b** isomers of the substrate.[128] It is therefore essential to suppress the isomerization in order to obtain high selectivities. The most successful reports from the literature are summarized in Table 29 with the chiral Xantphos-type ligand **134** providing the best results (Figure 8).[129]

The asymmetric Rh-catalyzed hydroformylation of dioxapines **135** was reported using the BINAPHOS ligand **77**.[124] Total regioselectivity toward aldehyde **136** was achieved, together with *ee*'s up to 76% Figure 8 (equation 32).

Table 25 Asymmetric hydroformylation of α-alkylacrylates



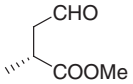
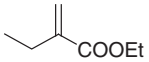
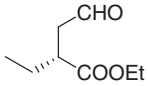
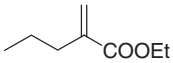
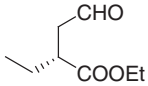
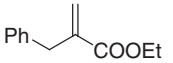
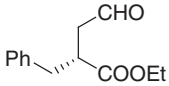
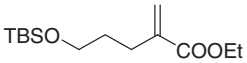
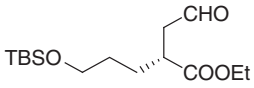
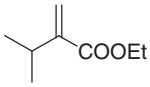
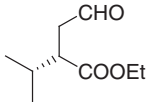
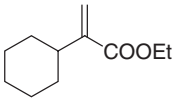
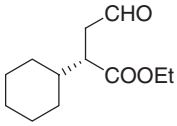
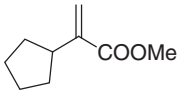
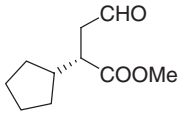
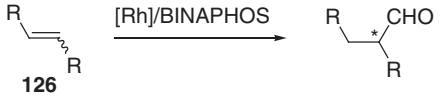
No.	*Substrate*	*Product*	*Yield (%)*	*ee (%)*
I			54	83
II			68	87
III			63	89
IV			60	84
V			62	81
VI			91	92
VII			84	94
VIII			85	93

Table 26 Rh-catalyzed asymmetric hydroformylation of symmetrical disubstituted alkenes



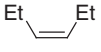
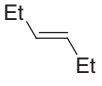
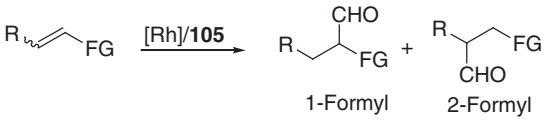
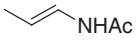
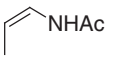
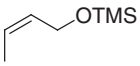
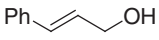
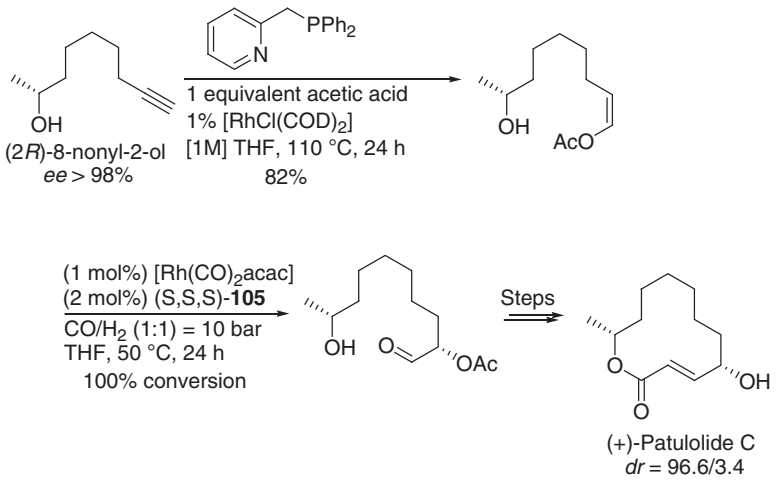
No.	*Olefin*	*ee (%)*
I		85
II		48
III		79
IV		69

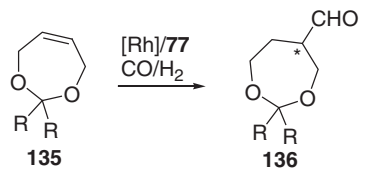
Table 27 Asymmetric hydroformylation of 1,2-disubstituted olefins



No.	*Substrate*	*Time (h)*	*Temperature (°C)*	*Conversion (%)*	*1-Formyl/2-formyl*	*ee (%)*
I		20	70	66	4.6/1	32
II		20	70	99	32/1	90
III		15	40	99	2.8/1	94
IV		16	80	99	1/50	90



Scheme 26



(32)

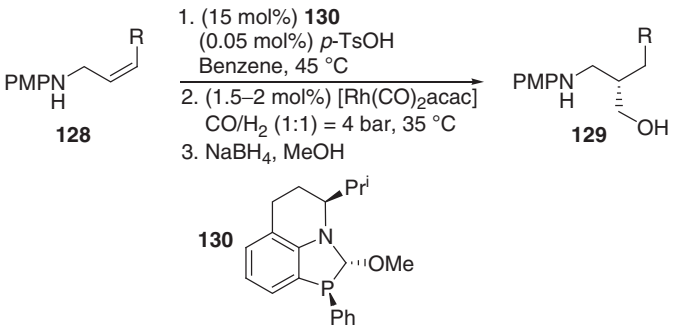
R = H		R = Me	
Regio (%)	*ee* (%)	Regio (%)	*ee* (%)
99	76	99	70

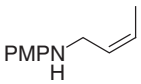
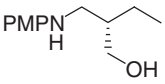
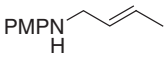
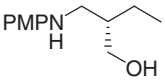
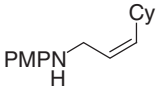
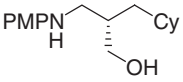
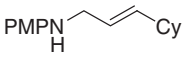
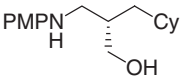
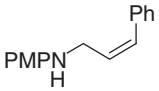
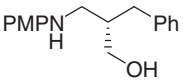
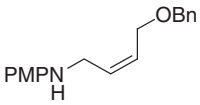
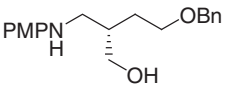
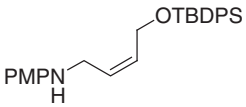
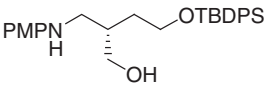
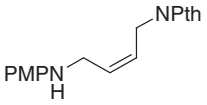
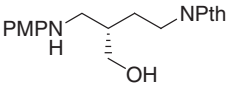
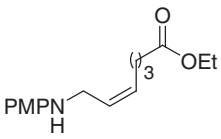
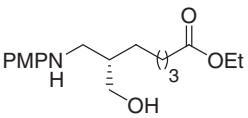
Enantioselective hydroformylation of dioxapines

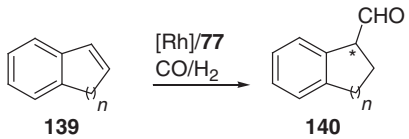
Recently, the first highly enantioselective Rh-catalyzed hydroformylation of norbornene **137** and derivatives has been developed. Applying diphospholane ligand **138**, the *exo* aldehyde could be obtained with *ee*'s up to 92% (Scheme 27).[130]

The benzoannulated bicyclic alkenes **139** allowed for regio- and enantioselective hydroformylation applying the rhodium/BINAPHOS catalyst system (equation 33). The corresponding α-aryl aldehydes **140** were formed in good to excellent enantioselctivities.[124] The corresponding products **140a** and **140b** are of interest since the aldehyde **140a** can be converted in a single step into the corresponding amine which exhibits hypotensive activity and the product **140b** is a synthetic intermediate to produce a vasoconstrictor tetrahydrozoline.[131]

Table 28 Enantioselective rhodium-catalyzed hydroformylation of allylic amines



No.	*Substrate*	*Product*	*Yield (%)*	*ee (%)*
I			69	92
II			74	80
III			75	86
IV			62	76
V			45	79
VI			70	92
VII			66	90
VIII			55	93
IX			68	96



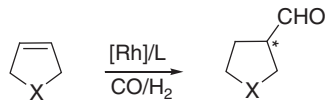
139 **140**

Product	*n*	Region (%)	*ee* (%)
140a	1	92	88
140b	2	96	97

(33)

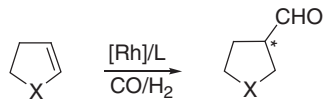
Enantioselective hydroformylation of bicyclic alkenes using (R,S)-BINAPHOS ligand **77**

Table 29 Asymmetric hydroformylation of five-membered heterocyclic alkenes



131a

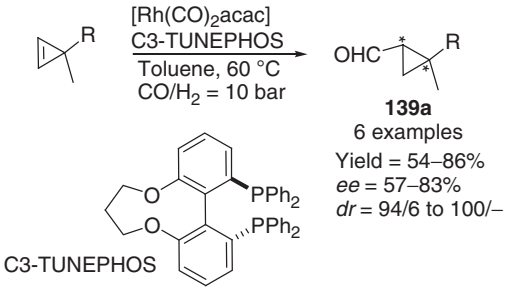
No.	*L*	*X*=*O*		*X*=*NBoc*		*X*=*NAc*	
I		Regio (%)	*ee* (%)	Regio (%)	*ee* (%)	Regio (%)	*ee* (%)
II	104	99	75			99	71
III	132	99	88				
IV	77	99	68	99	73	99	66
V	105			93	97		
VI	134	99	91				



131b

No.	*L*	*X*=*O*		*X*=*NBoc*	
I		Regio (%)	*ee* (%)	Regio (%)	*ee* (%)
II	104	76	75		
III	133	78	84		
IV	77	50	38	33	71
V	134	80	91		

Recently, the first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes was reported.[131b] The reaction proceeds under mild conditions and provides the corresponding cyclopropylcarboxaldehydes **139a** in good yields and enantio- and diastereoselectivities (equation 34).



(34)

Rh-catalyzed asymmetric hydroformylation of 3,3-disubstituted cyclopropenes

4.18.6 Hydroformylation of Alkynes, Allenes, and Epoxides

4.18.6.1 Hydroformylation of Alkynes

Although the hydroformylation of alkenes has been studied widely, the hydroformylation of alkynes has received significantly less attention. Most catalysts (cobalt and rhodium) so far reported furnished low selectivity and/or low yield of the corresponding unsaturated aldehydes. Major side products are the corresponding saturated aldehydes which may result from hydrogenation of the initially formed unsaturated aldehydes.[132] An alternative pathway toward the saturated aldehydes could be an alkyne hydrogenation followed by alkene hydroformylation which has been observed on reaction of certain terminal alkynes.[132]

An efficient catalyst for the chemoselective hydroformylation of symmetrical internal alkynes to furnish the α,β-unsaturated aldehydes in excellent yields under mild conditions is the rhodium(I)/BIPHEPHOS **19** catalyst (Table 30, entries I–V).[133] Furthermore, a bimetallic catalyst system consisting of $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$ was found to allow for hydroformylation of internal alkenes (Table 30, entries VI–X).[134]

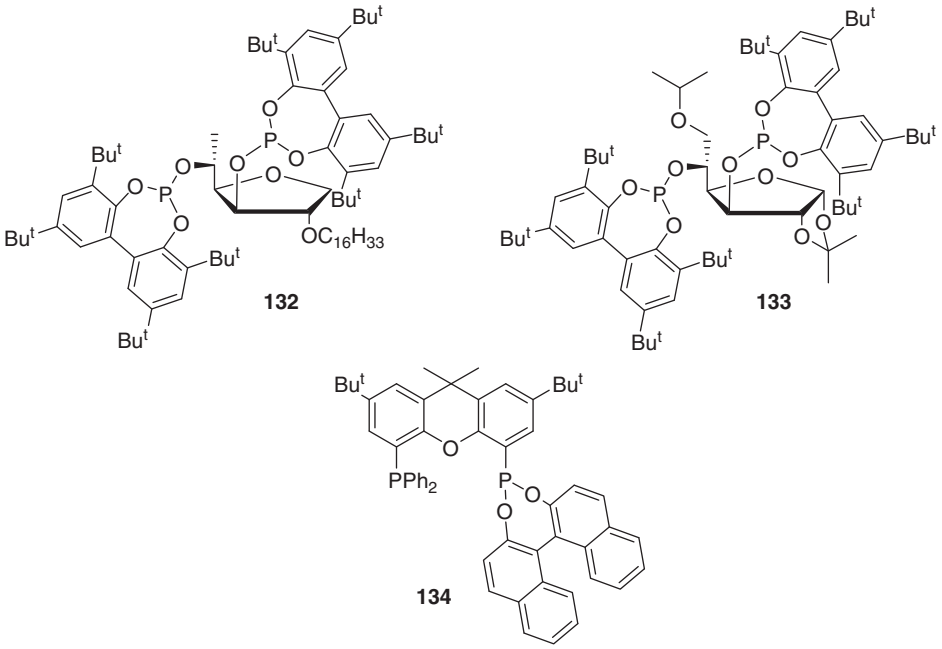
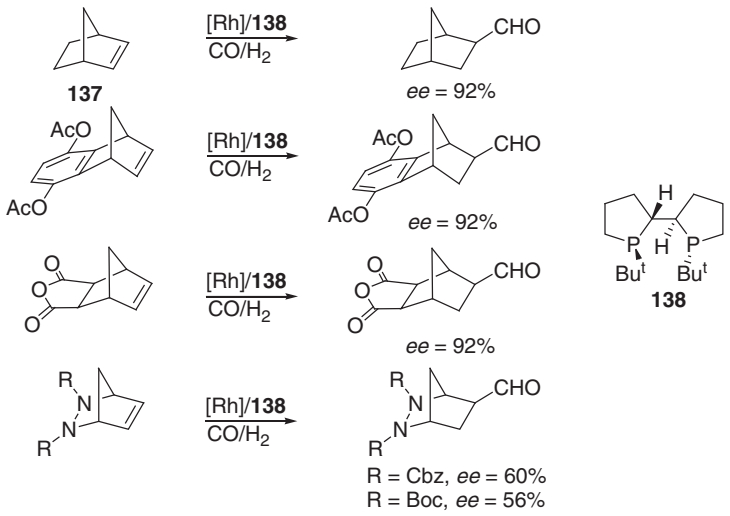


Figure 8 Ligands for enantioselective hydroformylation of 2,5-dihydrofurans and 2,5-dihydropyrroles **131**.



Scheme 27 Enantioselective hydroformylation of norbornene and its derivatives.

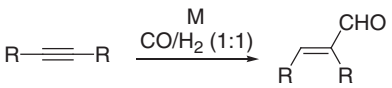
Although regioselective hydroformylation of unsymmetrical internal alkynes is not possible with the rhodium(I)/BIPHEPHOS catalyst, the bimetallic catalyst system showed good regioselectivity on hydroformylation of 1-cyclohexyl-1-propyne **141** to furnish (*E*)-3-cyclohexyl-2-methyl-2-propanal **142** predominantly in 52% isolated yield (Scheme 28). Similarly, the hydroformylation of 3,3-dimethyl-1-phenyl-1-butyne **143** by the $[PdCl_2(PCy_3)_2]$ catalyst gave exclusively (*E*)-4,4-dimethyl-2-phenyl-2-pentenal **144** (Scheme 28). The observed regioselectivity originates most likely from sterical effects.[134]

β-Alkynylamines **145** were found to undergo regioselective rhodium-catalyzed hydroformylation to give substituted pyrroles **146** in good yields (Table 31).[135] These reactions proceed through *α*,*β*-unsaturated aldehyde intermediates.

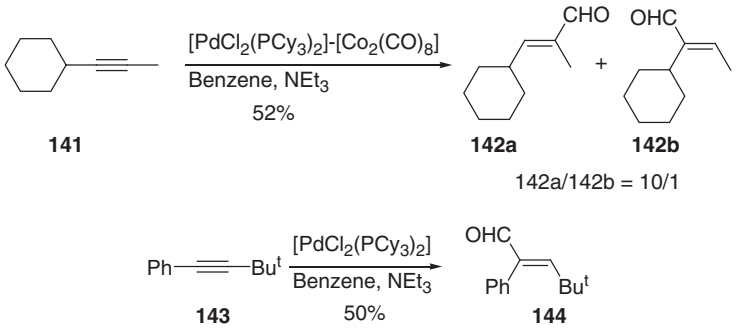
4.18.6.2 Hydroformylation of Allenes

Allenes have gained increased attention recently as reactive *π*-systems in transition metal catalysis. Conversely, not much is known on the reactivity of allenes under hydroformylation conditions. The first report on allene hydroformylation dates back to 1976. In this study, poor selectivities were observed furnishing a mixture of regioisomeric mono- and dialdehydes.[136] Controlling

Table 30 Hydroforymlation of internal alkynes

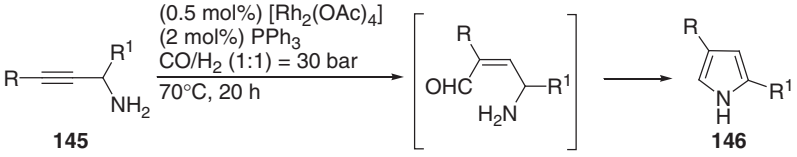


No.	*Conditions*	*R*	*GC yield (%)*
I	(2 mol%)[$Rh(CO)_2acac$]	*n*-Pr	96
II	(2.2 mol%) BIPHEPHOS	*n*-Et	92
III	CO/H_2 (1:1) = 1 bar	*n*-Bu	90
IV	CH_2Cl_2, r.t.	*n*-C_5H_{11}	92
V		Ph	56 (29% *Z*)
VI	(2 mol%) [$PdCl_2(PCy_3)_2$]/(1 mol%) [$Co_2(CO)_8$]	*n*-Pr	95
VII	CO/H_2 (1:1) = 75 bar	*n*-Et	88
VIII	Benzene, NEt_3, 150 °C, 1 h	*n*-Bu	90
IX		*n*-C_5H_{11}	95
X		Ph	53 (90% *E*)



Scheme 28

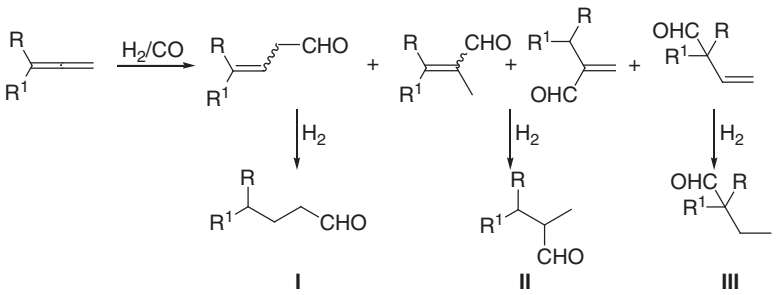
Table 31 Rhodium-catalyzed hydroformylation of β-alkynylamines



No.	*R*	*R^1*	*Pyrroles yield (%)*
I	Ph	H	85
II	Ph	Ph	96
III	Ph	Me	78
IV	*p*-Me-Ph	H	90
V	Bu	H	50

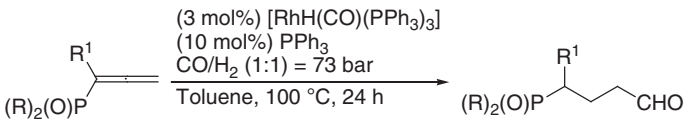
selectivity on hydroformylation of allenes is indeed a challenge. Thus, the hydroformylation of an allene may give rise to the formation of four different isomeric β,γ- or α,β-unsaturated enals which may undergo subsequent hydrogenation to furnish the corresponding saturated aldehydes I/II/III (Scheme 29).

Recently, the first example of the Rh-catalyzed highly regioselective hydroformylation–hydrogenation of 1,2-allenyl-phosphine oxides **147** and phosphonates was reported, yielding saturated linear γ-phosphinyl aldehydes **148** (Table 32), which are difficult to prepare using other methods.[137]



Scheme 29 The hydroformylation–hydrogenation of allenes.

Table 32 The hydroformylation–hydrogenation of 1,2-allenyl-phosphine oxides and -phosphonates



147 **148**

No.	R^1	*R*	*Yield (%)*
I	Pr^n	Ph	72
II	Bu^n	Ph	68
III	*n*-Hex	Ph	64
IV	Cyclopropyl	Ph	61
V	Pr^n	OEt	54
VI	Bu^n	OEt	59
VII	*n*-Hex	OEt	53
VIII	Cyclopropyl	OEt	50
IX	Ph	OEt	54

4.18.6.3 Hydroformylation of Epoxides

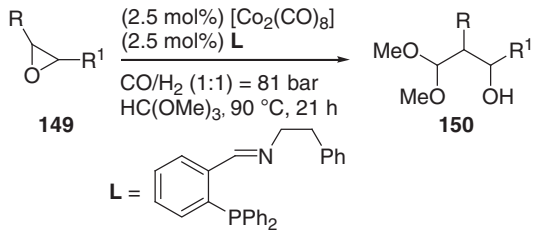
The cobalt-catalyzed hydroformylation of epoxides is an interesting method to furnish synthetically valuable β-hydroxyaldehydes, which may easily be hydrogenated to furnish 1,3-diols.[138] Typical side reactions are isomerization and hydrogenation. Previously, chelating diphosphine and hemilabile P–O ligands have been reported for the cobalt-catalyzed hydroformylation of epoxides.[139]

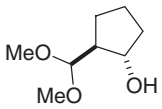
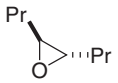
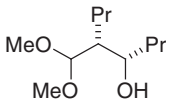
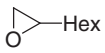
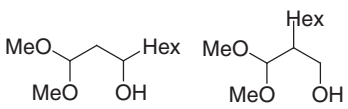
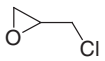
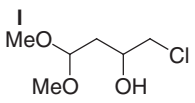
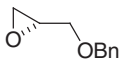
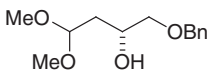
More recently, a variety of internal and terminal epoxides **149** were efficiently converted into protected β-hydroxyaldehydes **150** by highly regio- and stereoselective hydroformylation–acetalization using $Co_2(CO)_8$ as a catalyst in the presence of trimethyl orthoformate (Table 33).[140] The formylation of terminal epoxides was regioselective for the terminal position. Interestingly, the CO insertion into the epoxide C–O bond did proceed with inversion of configuration. Since epoxides are available in enantiomerically pure form by a number of processes, this reaction indeed is an interesting method to access β-hydroxy aldehydes in a stereospecific manner.

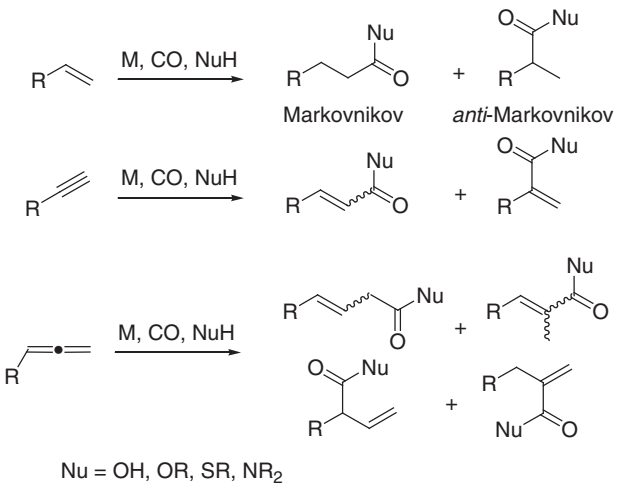
4.18.7 Related Carbonylation Reaction of Alkenes, Alkynes, and Allenes

Transition metal-catalyzed carbonylation of C/C π-systems in the presence of protic nucleophiles such as alcohols, amines, or thiols is a reductive carbon–carbon bond-forming reaction which furnishes C1-elongated esters, amides, or thioesters (Scheme 30). This transformation is complementary to hydroformylation since it provides carbonyl derivatives at the carboxylic acid oxidation state. The authors herein focus exclusively on reactions which are formally described as the 1,2 addition of a hydrogen and a carboxyl group across a C/C π-system. Although intense studies have been done during the past decades, this chemistry still lacks the level of selectivity control that can be reached today with hydroformylation chemistry. Thus, in this chapter only the synthetically most relevant examples which are complementary to hydroformylation chemistry have been included.

Table 33 Hydroformylation–acetalization of epoxides



No.	*Substrate*	*Product*	*Yield (%)*
I			74
II			13
III			69 l/b = 4.5
IV		**l**  **b**	33
V			52



Scheme 30 Carbonylation of alkenes, alkynes, and allenes.

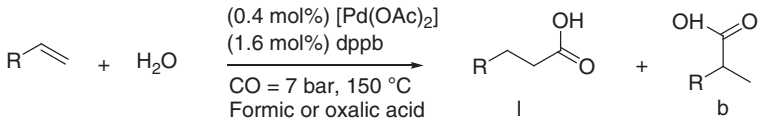
4.18.7.1 Carbonylation of Alkenes

4.18.7.1.1 Hydroxy- and alkoxycarbonylation

Carboxylic acids and their derivatives, such as esters and anhydrides, are important intermediates and products which have found pharmaceutical and agrochemical applications, among others.[141] There has been substantial interest in the synthesis of acids and

esters from vinyl aromatic compounds and the production of commodity chemicals from other readily available olefins[142] using the catalytic alkoxycarbonylation reaction, which is also known as the hydroesterification reaction. This reaction of alkenes generally requires a catalyst, such as palladium, and a Brønsted acid cocatalyst (usually *p*-toluenesulfonic acid (*p*-TsOH) or ($MeSO_3H$))[143] in the presence of carbon monoxide and alcohol. Metal halides of nickel, copper, iron, or cobalt have been used as the promoter, but, although these produce reasonable selectivities, fairly high catalyst loadings due to low catalyst activities are required.[144]

In 1969, the hydroxycarbonylation of terminal alkenes using phosphine-containing palladium complexes was patented for BASF.[145] Further studies[146] showed that $PdCl_2/PPh_3$ was a good catalyst precursor and the reaction parameters were optimized to achieve high activity and conversion combined with good regioselectivity toward the linear acid. Higher selectivity was obtained by using a mixture of palladium acetate $Pd(OAc)_2$, 1,4-bis(diphenylphosphinobutane (dppb), and formic or oxalic acid (equation 35).[147]



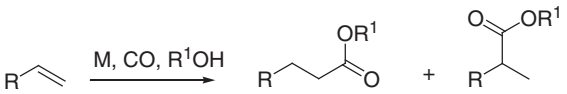
(35)

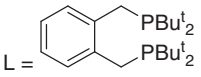
R = 1-Me-Phyield = 92%, l/b = 90/10
R = 2, 4, 6-Me_3-Ph yield = 98%, l/b = 100/-
R = $(Me)_3C$ yield = 94%, l/b = 100/-

Hydroxycarbonylation reaction of terminal alkenes

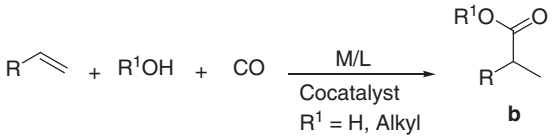
Alkoxycarbonylation of alkenes employing $[PdCl_2(PPh_3)_2]$ as catalyst precursor has been studied extensively.[148] Various terminal aliphatic alkenes are converted into the corresponding monoesters and the regioselectivity toward the linear ester can be improved by applying $SnCl_2$ as a cocatalyst.[148] A catalyst derived from $[Pd_2dba_3]$, bis(di-*tert*-butylphosphinomethyl)benzene, and methane sulfonic acid proved highly active for the methoxycarbonylation of terminal alkenes or the tandem isomerization–methoxycarbonylation of internal alkenes (2-octene, 3-octene, 4-octene, and 4-methyl-1-pentene) to linear carboxylic acid esters (**Table 34**, entry I).[149] A general, highly efficient and regioselective methoxycarbonylation, by means of a palladium–salicylicborate-catalyzed protocol, of terminal alkyl and aryl olefins was described. The substrates include aliphatic alkenes, allylbenzenes, and styrene derivatives (**Table 34**, entry II). The yields are good (60–92%) and the regioselectivity, in favor of the linear ester is up to quantitative.[150] Recently, the application of a strong, hydrolytically stable Lewis acid such as $Al(OTf)_3$ in the methoxycarbonylation reaction of styrene and 1-pentene has been shown to be favorable (**Table 34**, entry III).[151] This aluminum-based promoter significantly improves the activity of the catalyst, leading to rates 1.4–1.9 times higher than those observed for even the best benchmark Brønsted acids under comparable conditions.

Table 34 Linear-selective alkoxycarbonylation reaction of alkenes



No.	*Conditions*	*R*	*Conversion (%)*	*l/b*	*References*
I	(0.8 mol%) $[Pd_2(dba)_3]$, (4 mol%) L, CO = 1–4 bar, MeOH, CH_3SO_3H, 20 –80 °C, 3 h L = 	C_6H_{13}, C_5H_{11}, C_8H_{17}, Bu^i	71–100	94/6–99.9/0.1	149
II	(1.5 mol%) $[Pd(OAc)_2]$, (15 mol%) $(p\text{-tolyl})_3P$, CO = 27 bar, *p*-TsOH, MeOH, 100–110 °C, 18–22 h, (30 mol%)5-Cl-salicilic acid, (15 mol%) $B(OH)_3$	Alkyl, Ar. $ArCH_2$	100	85/15–100/0	150
III	(0.02 mol%) $[Pd(OAc)_2]$, (0.36 mol%) PPh_3, CO = 50 bar, MeOH, 100 °C, 3 h, (0.36 mol%) $Al(OTf)_3$	Ph, Pr^n	100	75/25–78/22	151

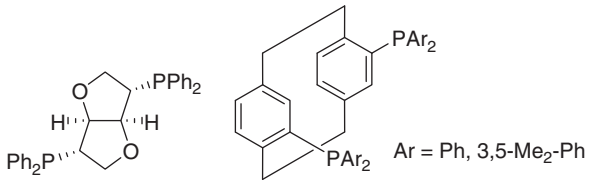
It was shown that the selectivity of the hydroxycarbonylation reaction can be steered toward the branched acid by adding copper (II) chloride and hydrochloric acid to the palladium catalyst [$PdCl_2$].[152] Similarly, good selectivity for the branched isomer has been achieved using the water-soluble palladium (II) tosylate complex containing a chelating anionic ligand such as 2-carboxylatopyridine or $PdCl_2$/trisulfonated triphenylphosphine (TPPTS).[153] At 30 bar, in water 2-aminophenylthiolato ligands coordinated to $PdCl_2$ moieties allow complete regioselectivity toward the branched acid, in the hydroxycarbonylation of styrene.[154] The methoxycarbonylation of alkenes catalyzed by palladium(II) complexes with P,N-donor ligands, such as 2-(diphenylphosphinoamino)pyridine (Ph_2PNHpy), has been also investigated. This catalytic system promotes the conversion of styrene in 98% regioselectivity toward the branched isomer. This catalyst was also efficient in the methoxycarbonylation of cyclohexene and 1-hexene, although with lower rates than with styrene.[155]



(36)

Branched selective carbonylation reaction of alkenes

An enantioselective variant of alkene carbonylation is potentially the most efficient and versatile method to obtain single-enantiomer carboxylic acid derivatives, and both hydroxycarbonylation[156] and methoxycarbonylation[142] have attracted attention for many years. The reaction has not been widely used in synthesis due to the difficulty of obtaining simultaneously both high regio- and enantioselectivities, and the low overall yield of the branched isomer. However, important contributions to this field were reported including some reports of very good enantioselectivity. The use of several chiral diphosphines,[157] monophosphines,[158] and hemilabile ligands[157m,159] was reported for the asymmetric alkoxycarbonylation of styrene and its derivatives but only moderate regioselectivity and/or *ee* were achieved. The first reports of asymmetric alkoxycarbonylation of vinylarenes (styrene and α-methylstyrene) appeared in the 1970s using DIOP as ligand.[157] In 1997, a $PdCl_2$/$CuCl_2$/chiral diphosphine **151** (DDPPI) system (Figure 9) was described to achieve 98% *ee* and 99% regioselectivity to the branched ester for the methoxycarbonylation of styrene at 80 °C under 50 bar of CO.[157] Using the $Pd(OAc)_2$/DDPPI/*p*-TsOH catalytic system for the methoxycarbonylation of norbornene, 92% *ee* was obtained under 50 bar of CO at 120 °C.[157] Recently, a dinuclear palladium complex based on the bridging phanephos ligand **152** was found to enable a highly enantioselective albeit regioselectivity was mediocre (Figure 9).[160] The same catalyst system was used for the hydroxycarbonylation of norbornene. High conversion, moderate chemoselectivty (50–65%), excellent *ee* (95%), and high *exo*/*endo* ratio up to 93/7 were obtained.



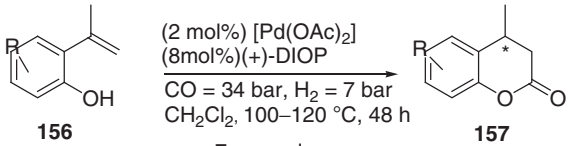
151
ee = 98%
b/l = 99/1

152
ee = 91%
b/l = 49/51

Figure 9 Chiral ligands for enantioselectives palladium catalyzed alkene carbonylation.

The intramolecular carbonylation of hydroxy functionalized alkenes with CO in the presence of transition metal compounds yields lactones. Palladium catalysts have been used mainly for these cyclization reactions and five-, six-, and seven-membered lactones were successfully obtained.[161] The asymmetric version of this reaction was also studied. The best enantioselectivity achieved so far was obtained, using Pd/BICP [2*R*,2*R*-bis-(diphenylphosphino)-1*R*,1*R*-dicyclopentane] **155** catalyst for the intramolecular carbonlyation of geminally disubstituted allylic alcohols **153** and β,γ-substituted allylic alcohols **154** (Scheme 31).[162]

Intramolecular carbonylation of *o*-isopropenylphenols **156** was also described using $Pd(OAc)_2$ and (+)-DIOP as the chiral catalyst (equation 37). The corresponding bicyclic lactones (3,4-dihydro-4-methylcoumarins) **157** were formed in high yields and enantioselectivities up to 90%.[163]



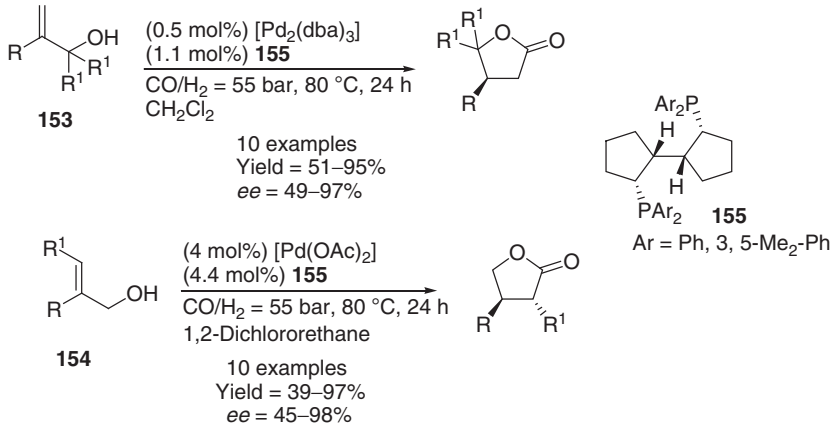
156

7 examples
Yield = 65–85%
ee = 15–90%

157

(37)

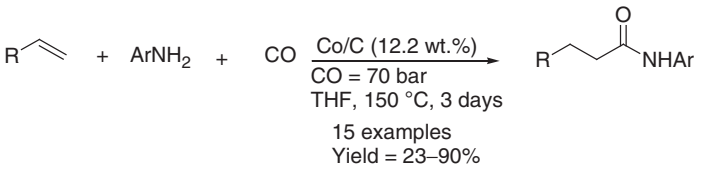
Palladium-catalyzed asymmetric intramolecular carbonylation of *o*-isopropenylphenols



Scheme 31 Enantioselective intramolecular carbonylation of geminally disubstituted and β,γ-substituted allylic alcohols.

4.18.7.1.1.1 Aminocarbonylation

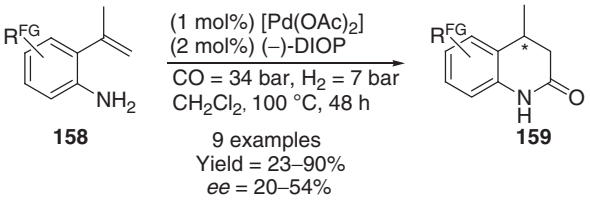
Carbonlyation of alkenes in the presence of amines furnishes amides in an atom-economic fashion and could eventually be a highly attractive synthetic method for amide bond formation. However, only little is known in this area. Thus, amidocarbonylation of terminal alkenes in the presence of aniline derivatives was achieved employing cobalt on charcoal catalyst (equation 38).[164]



(38)

Amidation of various alkenes with aniline derivatives

The intramolecular carbonylation of 2-vinyl- and 2-allylanilines employing palladium catalysts furnishes five-, six-, and seven-membered lactams.[161t] The asymmetric version of this reaction for the synthesis of optically active benzofused lactams was also reported using palladium catalysts (equation 38). Thus, employing a palladium/(–)-DIOP catalyst the asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines **158** proceeded in up to 54% *ee* to give 4-methyl-3,4-dihydroquinolin-2-one derivatives **159** (equation 39).[165]



(39)

Asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines

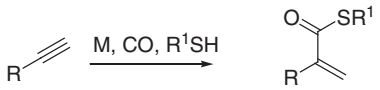
4.18.7.2 Carbonylation of Alkynes

4.18.7.2.1 Thiocarbonylation

The use of transition metal complexes as homogeneous catalysts in reactions involving organosulfur compounds as substrates has been the subject of relatively few investigations, because the strong thiophilicity of transition metals[166] may make catalytic reactions ineffective. However, the search for new methods for the preparation of thiol esters and sulfur-containing γ-lactones is a topic of current interest.[167] These compounds constitute a group of natural products,[168] and they are also attractive building blocks in the synthesis of complex organic molecules.[166] Highly selective thioformylation and hydrothiocarbonylation of alkynes with carbon monoxide and thiols in the presence of rhodium, platinum, palladium, and cobalt catalysts represent one of the most straightforward routes to these compounds.

When $[Pd(OAc)_2]$/dppp or $[Pt(PPh_3)_4]$ are used as catalysts, a highly regioselective hydrothiocarbonylation occurred to furnish the thioesters with complete *anti*-Markovnikov selectivity (Table 35).

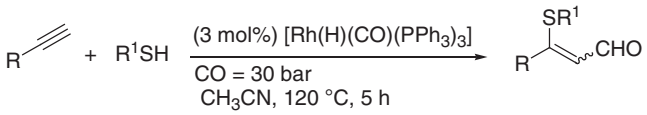
Table 35 Hydrothiocarbonylation of terminal alkynes



anti-Markovnikov

No.	*Conditions*	*R^1*	*R*	*Yield (%)*	*References*
II	(3 mol%) $[Pt(PPh_3)_4]$ CO = 30 bar, CH_3CN, 120 °C, 1–7 h	Ph, *p*-F-Ph, *p*-MeO-Ph, *n*-C_8H_{17}, *c*-C_6H_{11}, $CH_3(CH_2)_{11}$	*n*-C_6H_{13}, $(CH)_3CH(CH_2)_2$, Ph, CH_2Ph, $NC(CH_2)_3$	61–99	169
III	(1 mol%) $[Pd(OAc)_2]$, (4 mol%) dppp, CO = 21 bar, *p*-TsOH, THF, 110 °C, 6 h	R = Ph, *p*-Me-Ph	Pr^n, C_5H_{11}, $(CH_3)_3C$, $NC(CH_2)_3$, Ph	71–100	170

Conversely, with $[Rh(H)(CO)(PPh_3)_3]$ as catalyst highly regioselective thioformylation of alkynes with thiols and carbon monoxide was observed (equation 40).[171] Indeed, the insertion of the thio and formyl groups occur at the inner and terminal positions of the alkynes, respectively.

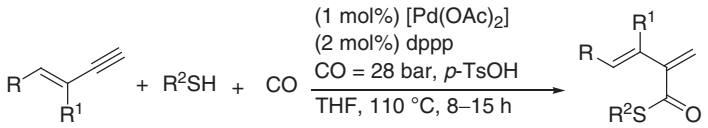


9 examples
Yield = 23–82%
E/*Z* = 41/59–1/99

(40)

Rhodium-catalyzed thioformylation of terminal alkynes

A highly regio- and chemoselective hydrothiocarbonylation of terminal enynes **160** was described with $[Pd(OAc)_2]$/dppp as catalyst (equation 41). The α,β-unsaturated thioesters **161** were obtained in moderate to good yields.[172]



160

13 examples
Yield = 33–76%

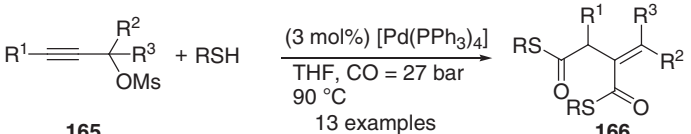
161

(41)

Hydrothiocarbonylation of terminal enynes

Thiophenols react with propargylic alcohols **162** in the presence of $[Pd(PPh_3)_4]$ catalyst to afford β-(arylthio)-α,β-unsaturated lactones **163** or β,γ-unsaturated thioesters **164**, depending on the reaction conditions (Scheme 32).[173]

The same catalyst was used for the highly stereoselective dithiocarbonylation of propargylic mesylates **165** with thiols and carbon monoxide.[174] The reaction affords the corresponding dithioesters **166** in good to excellent yields (equation 42). It was shown that for some secondary and tertiary propargylic alcohols with a terminal or internal triple bond, the reaction stereoselectively produces the *E*-dithioesters as the only products.



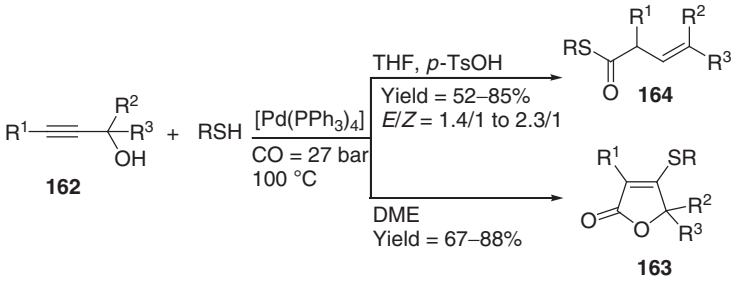
165

13 examples
Yield = 57–91%

166

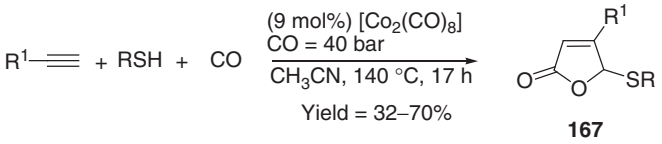
(42)

Dithiocarbonylation of propargylic mesylates



Scheme 32 Palladium-catalyzed carbonylation of propargylic alcohols.

Recently, $[Co_2(CO)_8]$ catalyst was used for the thiolative lactonization of alkynes with simultaneous introduction of two CO molecules into the carbon–carbon triple bonds to afford α,β-unsaturated γ-thio-γ-lactones **167** with good regioselectivity (equation 43).[175]



(43)

$Co_2(CO)_8$-catalyzed thiolative lactonization of terminal alkynes with double CO incorporation

4.18.7.2.1.1 Aminocarbonylation

α,β-Unsaturated amides are an important class of compounds because of their biological and insecticidal activities,[176] their presence in the structure of natural products,[177] and their role as a reaction partner in many useful transformations.[178] The most desirable method for preparing α,β-unsaturated amides would be a direct carbonylation of alkynes in the presence of amines, i.e., aminocarbonylation. Various palladium-catalyzed aminocarbonylation reactions are known.[179]

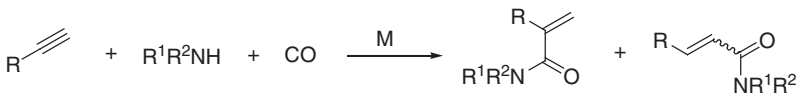
The $Pd(OAc)_2$/dppp-catalyzed aminocarbonylation of alkynes with amines in ionic liquid [bmim][Tf_2N] under mild conditions has been reported (**Table 36**, entry I).[180] Acrylamides **168** were obtained in good yields; however, the catalytic system is ineffective for the aminocarbonylation of internal alkynes. The same catalyst system allows for carbonylation of alkyl and aryl alkynes with aniline derivatives (**Table 36**, entry II).[181]

Recently, iron-catalyzed aminocarbonylation of internal and terminal alkynes has been developed (**Table 36**, entry III). The *anti*-Markovnikov cinnamide and acrylamide products **169** were obtained in high chemo- and regioselectivity. In contrast to the results obtained with palladium, the iron catalyst gives the linear *E*-amides as the main products (selectivity >90%).[182] However, in the case of diphenylacetylene, both *Z* and *E* isomers were isolated (*Z*/*E* = 1.2/1). (*E*)-Cinnamide was isolated as the main product in a ratio (10/1 = Markovnikov **168**/*anti*-Markovnikov **169**). The monocarbonylation would take place by a stepwise mechanism. For this latter process the authors propose that an iron hydride carbonyl cluster ([Fe]–H) reacts with the alkyne followed by subsequent formation of an acylcarbonyliron complex and nucleophilic attack by the amine should lead to the formation of acrylamide and regeneration of the active iron species.

The aminocarbonylation of disubstituted alkynes was accomplished employing Co_2Rh_2 heterobimetallic nanoparticles in the presence of CO and amines (**Table 37**). This reaction could be carried out under relatively low CO pressure and the catalytic system did not require any additives or promoters such as phosphines or ionic liquids.[183]

So far, very limited work has been done toward carbonylative coupling of primary and secondary amines with internal alkynes.[184] Recently, a selective double aminocarbonylation reaction of internal alkynes toward the synthesis of 3-(hetero)-aryl-4-arylsuccinimides and maleimides employing $Fe_3(CO)_{12}$ as catalyst was reported (equation 44). Terminal alkynes showed lower reactivity. It was proposed that the succinimide formation proceeds by a concerted double insertion of CO.[185]

Table 36 Aminocarbonylation of alkynes



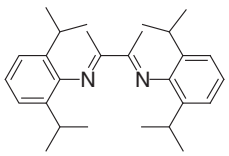
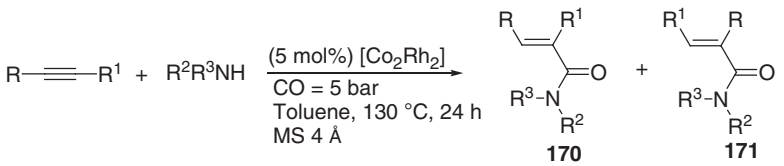
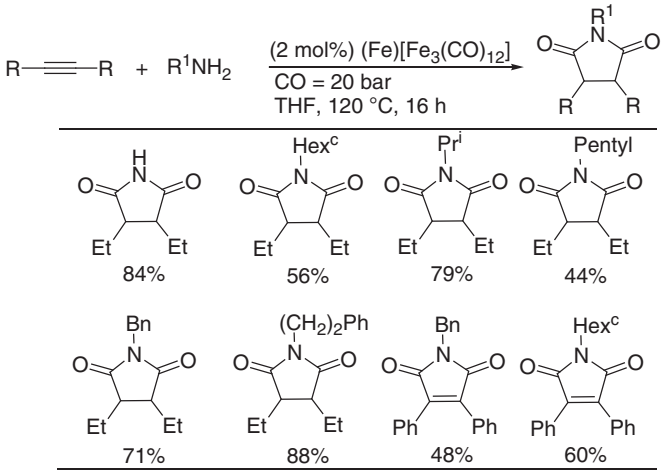
No.	Conditions	R	Amines	Yield (%)	168/169	References
I	(3 mol%) $[Pd(OAc)_2]$, (6 mol%) dppp, CO = 14 bar, $[Bmim][Tf_2N]$, 110 °C, 22 h	Bu^n, n-C_6H_{13}, $AcO(CH_2)_4$, Ph, $PhS(CH_2)_2$, $NC(CH_2)_3$, $CH(OEt)_2$	Aniline, benzylamine, diethylamine, butylamine, pyrrolidine, morpholine aniline, 2,4-Me-aniline, 4-Cl-aniline, *N*-methylaniline, *N*-ethylaniline, diisobutylamine pyrrolidine, cyclohexylamine, piperazine , cyclooctylamine, 2-phenylethylamine, 2-methoxyethylamine	50–85	>99/1	180
II	(1 mol%) $[Pd(OAc)_2]$, (2–4 mol%) dppp, CO = 20 bar, *p*-TsOH, THF or CH_3CN, 110 °C, 6–15 h (5 mol%)Fe $[Fe_3(CO)_{12}]$, (5 mol%) L, CO = 10 bar, THF, 120 °C, 16 h	Pr^n, n-C_5H_{11}, n-C_7H_{15}, $(CH_3)_3C$, $NC(CH_2)_3$,Ph n-C_6H_{13}, Ph, Hex^c, 3,5-$(MeO)_2$Ph, 2-Me-Ph, 2-MeO-Ph, 4-CF_3-Ph, 2,4-(Me)(OMe)-Ph, 4-Me_2N-Ph		71–100	84/16–100/0	181
III	L = 			58–95	0/100	182

Table 37 Co_2Rh_2-catalyzed aminocarbonylation of internal alkynes



No.	Alkyne	Amine	Yield (%)	170/171
I	R = R^1 = Et, Pr, Ph	Butylamine, octylamine, benzylamine, diethylamine, dodecylamine, cyclohexylamine	24–85	–
II	Ph—≡—Et	Butylamine	75	1.1/1
III	Ph—≡—Bu	Butylamine	81	1.5/1
IV	Ph—≡—C_6H_4OMe	Butylamine	48	1.2/1

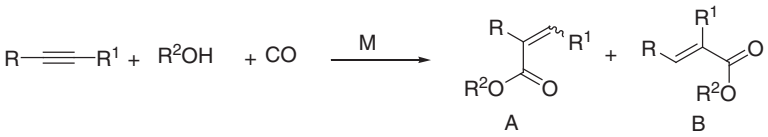


(44)

Carbonylation of various internal alkynes

4.18.7.2.1.2 Hydroxy- and alkoxycarbonylation

Carbonylation of acetylene is one of the first examples of Reppe carbonylation by metal complexes. This reaction allows for a highly attractive atom-economic and direct access to α,β-unsaturated acids and esters from alkynes. Palladium-based catalyst systems such as $Pd(PPh_3)_4$, $Pd(OAc)_2$/dppf,[186] $Pd(OAc)_2/PPh_3$/dppb,[187] and $Pd(dba)_2/4PPh_3$[188] have been demonstrated to catalyze the carbonylation of alkynes at lower CO pressures (1–20 bar), with rather low activity as a major limitation.



(45)

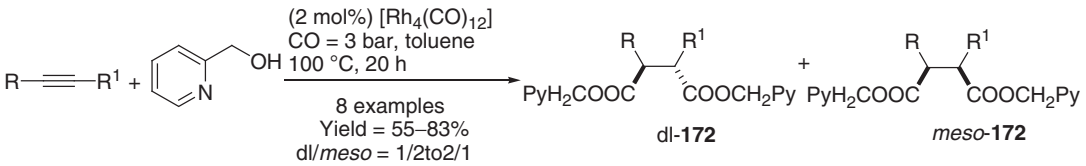
Alkoxycarbonylation reaction

Highly efficient carbonylation of terminal and internal alkynes have been reported, in which palladium(II) catalysts modified with 2-pyridylphosphine, bisphenyl-(6-methyl-2-pyridyl)phosphine, 2-pyrimidylphosphines, or pyridine-2-carboxylic acid/PPh_3 ligands and acidic promoters were used.[189] These reports indicate the importance of P/N ligands to furnish high catalyst activity for the carbonylation of higher alkynes (**Table 38**, entries I–III).

Another useful catalyst system is the $Pd(OAc)_2$/BINAP/$Al(OTf)_3$ combination, which allows for methoxycarbonylation of phenylacetylene to provide the branched ester product in high yield and selectivity. This catalyst could be recycled 10 times, with only small losses of activity and selectivity (**Table 38**, entry IV). In the present system, the Lewis acid cocatalyst $Al(OTf)_3$ proved superior in terms of catalyst activity compared with Brønsted acids under identical conditions.[190]

Palladium(II) and 1,4-bis(diphenylphosphino)butane in the presence of a mixture of salicylic and boric acids (BSA) in acetonitrile was an effective and selective catalyst system for the regioselective alkoxycarbonylation of phenylacetylene toward *trans*-α,β-unsaturated ester (*anti*-Markovnikov product) (**Table 38**, entry V).[191] The palladium-catalyzed alkoxycarbonylation of internal alkynes in the presence of phenol and zinc as cocatalyst furnished the corresponding α,β-unsaturated arylesters in good yield and regioselectivity (**Table 38**, entry VI).[192]

The reaction of internal alkynes with CO and pyridin-2-ylmethanol in the presence of $Rh_4(CO)_{12}$ results in a double-hydroesterification leading to 1,4-dicarboxylate esters **172** (equation 46). The chelating ability of the pyridine nitrogen to rhodium proved essential for the reaction to proceed.[193]

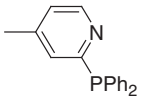
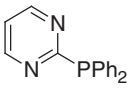
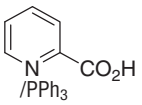


(46)

$Rh_4(CO)_{12}$-catalyzed carbonylation of alkynes with CO and pyridin-2-ylmethanol

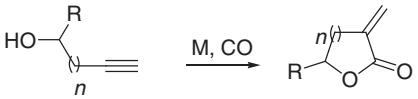
Methylene lactones deserve special interest due to their presence in many biologically active natural products.[194] Unsaturated lactones can be obtained through intramolecular alkoxycarbonylation of alkynols.

Table 38 Alkoxycarbonylation of internal and terminal alkynes

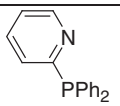
No.	Conditions	Ligand	R	R^1	R^2	Yield (%)	A/B	References
I	(0.06 mol%) $[Pd(OAc)_2]$, (0.24 mol%) L, CO = 60 bar, 60 °C, *p*-TsOH, 2 h		Pr^n	H	Me	99	99.95	189
II	(0.06–0.31 mol%) $[Pd(OAc)_2]$, (0.22 mol%) L, CO = 60 bar, 60 °C, 2 h, methanesulfonic acid		Bu^n, Bu^t, Ph	H	Me	83–97	100/-	189
III	(0.2 mol%) $[Pd(OAc)_2]$, (6 mol%) PPh_3, CO = 2 bar, *p*-TsOH, toluene, 100 °C, 0.16 –2.4 h		CH_3–Ph, Ph, Me, C_6H_9, CH_2OH	H, Ph	C_4H_9	50–90	47/53 to 97/3	189
IV	(0.1 mol%) $[Pd(OAc)_2]$, (0.4 mol%) L, CO = 35 bar, 82 °C, $Al(OTf)_3$	BINAP	Ph	H	Ph	99	99/1	190
		BINAPS	Ph	H	H	100	100/-	190
V	(1 mol%) $[Pd(OAc)_2]$, (4 mol%) L, CO = 14 bar, 90 °C, 3 h, salicylic acid, $B(OH)_3$, CH_3CN	dppb	Ph	H	Me, Et, Pr, Bu, Hex, Oct	99–100	11/89 to 8/92	191
VI	(5 mol%) $[Pd(OAc)_2]$, (5 mol%) L, CO = 1 bar, toluene, 100 °C, 24 h, Zn	dppp	*n*-C_6H_{13}, Ph, Pyridyl CO_2Et, $SiMe_3$, Me	Me Ph	Ph	44–98	36/64 to -/100	192

Different palladium precursors such as $PdI_2/PBu_3/CH_3CN$ or $PdCl_2/PPh_3/SnCl_2/CH_3CN$ have been developed as efficient catalysts to carbonylate alkynols **173** toward α-methylene lactones **174** under mild conditions.[195] Furthermore, $Pd(OAc)_2$/2-$PyPPh_2$ is an effective catalyst for the intramolecular alkoxycarbonylation of alkynols, leading exclusively to five- or six-membered *exo*-methylene lactones (Table 39, entry I). This catalytic system can also be immobilized in ionic liquids such as $BMI \cdot BF_4$ and $BMI \cdot PF_6$ (liquid–liquid biphasic conditions) without any changes in catalytic activity or selectivity.[196] Moreover, $[Pt(PPh_3)_4]$ has been shown to catalyze the lactonization of 5-hydroxy-1-pentyne toward the formation of α-phenylthiomethyl-δ-lactone with yields improved by the presence of arylthiols (Table 39, entry II).[197] Indeed, the oxidative addition of the S–H bond on platinum is easier than that of the O–H bond, and can trigger the catalytic cycle more efficiently.

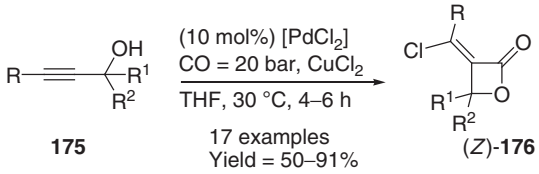
Table 39 Intramolecular alkoxycarbonylation of alkynols



173 **174**

No.	Conditions	Ligand	n	Yield (%)	References
I	(1 mol%) $[Pd(OAc)_2]$, (1 mol%) L, CO = 25 bar, 60 °C, 2 h, toluene		1,2	50–99	197
II	(3 mol%) $[Pt(PPh_3)_4]$ CO = 30 bar, MeCN, 120 °C, 4 h, ArSH	–	2	32–76	198

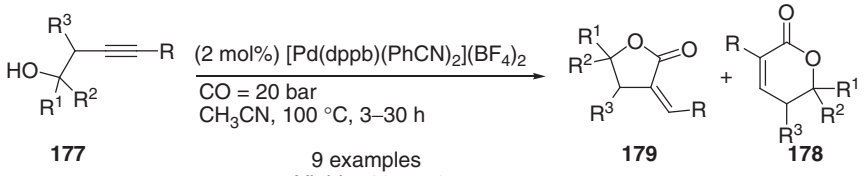
A mild and efficient Pd-catalyzed cyclocarbonylation of alkynols **175** was carried out in the presence of a large excess of $CuCl_2$ (5 equivalents), to furnish (*Z*)-α-chloroalkylidene-β-lactones **176** (equation 47).[198] The introduction of the halide substituent is supposed to occur through a *cis*-chlorometalation of the alkyne. (*Z*)-α-Bromoalkylidene-β-lactones can be similarly obtained when using $Pd(OAc)_2$ and $CuBr_2$. Starting from readily available optically active propargylic alcohols enables a convenient preparation of the enantiomerically pure corresponding (*Z*)-α-chloroalkylidene-β-lactones.



(47)

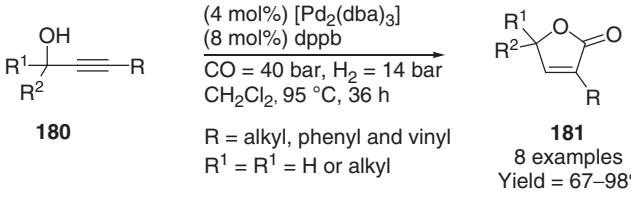
Palladium-catalyzed secondary and tertiary propargylic alcohols

Unsaturated lactones containing an endocyclic double bond from the cyclocarbonylation of 3-butyn-1-ols **177** catalyzed by cationic palladium complexes has been studied. Six-membered ring lactones **178** were produced preferentially in acetonitrile using cationic complexes coordinated by certain chelating diphosphines as catalyst $[Pd(PhCN)_2(dppb)]^+BF_4^-$(equation 48). It is suggested that the mechanism involves a cationic palladium-hydride that coordinates to the triple bond; then a hydride transfer occurs through a *cis*-addition and lead to the formation of six-membered ring lactones.[199]



(48)

Alternatively, the addition of dihydrogen to the palladium(0) precursor $Pd_2(dba)_3$/dppb affords an 'active' system, to undergo direct carbonylation of a series of substituted alkynols **180** containing alkyl, phenyl, and vinyl groups at the acetylenic terminal, to the corresponding substituted 2(5*H*)-furanones **181** in good yield (equation 49).[200]

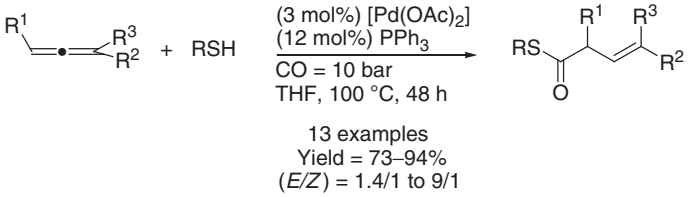


(49)

Palladium-catalyzed cyclocarbonylation of alkynols

4.18.7.3 Carbonylation of Allenes

Palladium catalysts such as $Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$ are effective for the thiocarbonylation of allenes with thiols and carbon monoxide. The reaction is completely regioselective. Thus, thiocarbonylation occurs at the less-substituted double bond of the allene to give the β,γ-unsaturated thioester in good yields (equation 50). A series of mono and disubstituted allenes were explored and in all cases good yields were obtained.[201]

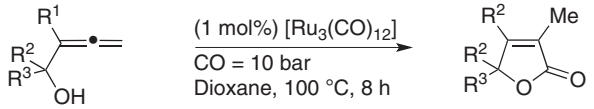


(50)

Palladium catalyzed thiocarbonylation of allenes

Although intramolecular alkoxycarbonylation of alkenes and alkynes furnishing γ-lactones have been extensively studied, only few examples of the intramoleclar alkoxycarbonylation of allenes have been reported. Thus, starting from allenyl alcohols **182** a

ruthenium-catalyzed intramolecular oxycarbonylation lead to the corresponding γ- and δ-lactones **183** in excellent yields (equation 51). The reaction is applicable to a wide variety of allenyl alcohols, such as mono-, di-, and trisubstituted allenyl systems to afford 3- and 4-substituted γ-lactones. Similarly, the cyclic carbonylation of 3,4-pentadien-1-ol and 2-methyl-4,5-hexadien-2-ol gave the corresponding δ-lactones in a quantitative yield.[202] A related chlorocarbonylation of allenyl alcohols has also been reported.[203]



182 11 examples Yield = 91–99% **183** (51)

R^1 = H, OMe
$R^{2,3}$ = H, alkyl, phenyl

Carbonylation of allenyl alcohols

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4.19 Methylene and Nonfunctionalized Alkylidene Transfer to Form Cyclopropanes

AB Charette, Université de Montréal, Montreal, QC, Canada

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Glossary

Carbenes Molecule containing a neutral carbon atom with a valence of two and two valence electrons.

Carbenoids Reactive intermediate of general formula $R^1R^2C(X)M$ (M = metal) that displays a reactivity similar to a carbene.

Chiral auxiliary Chiral subunit that is temporarily covalently incorporated into an organic substrate to control the stereochemical outcome of a reaction.

Metal carbenes Organometallic compounds that comprise a metal and a divalent carbene.

Ylides Neutral molecule containing a formally negatively charged atom directly attached to a hetero atom with a formal positive charge.

4.19.1 Introduction

4.19.1.1 Scope

The cyclopropane unit has generated interest over the years through its unique bonding properties, its rigidity, its numerous applications in diverse chemical transformations, and its importance in natural product synthesis and in drug development. Several reviews describing its uses and the various approaches for its preparation have appeared.[1] This chapter highlights the most important methods since 1989 to prepare substituted cyclopropane derivatives from alkenes. The coverage of the chapter includes all the following general strategies (Scheme 1): (1) ring contraction of pyrazolines obtained from an alkene by a [3+2] dipolar cycloaddition of a diazoalkane, (2) cyclopropanation of alkenes with metal carbenes; (3) cyclopropanation of alkenes with metal carbenoids (MCH_2X), and (4) Michael-initiated ring closure. Emphasis will be placed on methods that allow the preparation of diastereo- and enantiomerically enriched cyclopropane derivatives.

The literature covered in the previous edition of Comprehensive Organic Synthesis will not be included unless the topic is absolutely necessary to understand the more recent advances in the proper context. As in the previous edition, the following important material will be presented elsewhere: (1) transfer of 1,1-dihalocarbenes, (2) transfer of other hetero-substituted alkylidene groups, (3) cyclopropanation using diazo compounds bearing at least one electron-withdrawing group,

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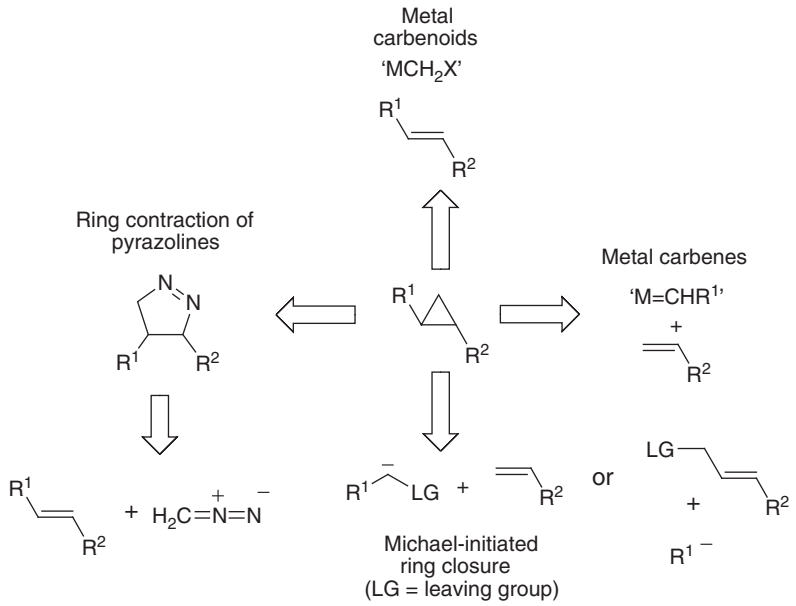


Scheme 1

(4) Michael-induced ring closure of stabilized ylides, (5) transfer of other functionalized alkylidene groups when these reactions are dependent on this functionalization, (6) direct 1,3-coupling reactions, (7) intramolecular C–H insertions of carbenes, (8) ring contraction and other rearrangements, (9) generation of vinyl- or divinyl cyclopropanes as intermediates directed specifically toward the synthesis of cyclopentenes or cycloheptadienes, (10) synthesis of alkylidene cyclopropanes, (11) synthesis of cyclopropenes and the preparation of cyclopropanes from cyclopropenes, and (12) the Kulinkovich reaction.

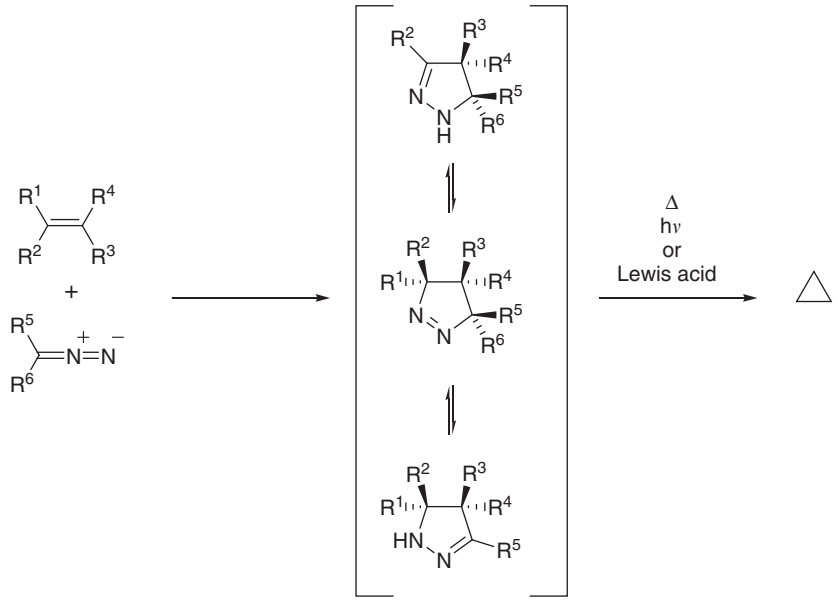
4.19.2 Cyclopropanation by Ring Contraction of Pyrazolines

Diazoalkanes have been one of the reagents of choice to generate cyclopropanes from alkenes. Two classes of reactions emerged from these reagents. The first, in which the diazoalkane reagent is converted into a metal carbene or carbenoid, will be reviewed in following sections; the second, in which an initial [3+2] cycloaddition takes place followed by a subsequent nitrogen extrusion, will be reviewed in this section (Scheme 2). The [3+2] cycloaddition reaction is a concerted process that is much faster if the alkene bears electron-withdrawing substituents. Because of the sensitive nature of diazoalkanes, these reactions have been carried out on relatively small scales. The decomposition of the initially formed pyrazolines via nitrogen extrusion can be accomplished under thermal, photochemical, or Lewis acid-catalyzed conditions. The preparation of chiral cyclopropane derivatives by pyrolysis of pyrazolines is usually quite problematic due to the easy olefin isomerization. In some cases, the addition of Lewis acids or carrying the nitrogen extrusion under photochemical conditions significantly increases the amount of cyclopropane. Numerous examples were provided in the first edition of this series and therefore the discussion here will be minimal.

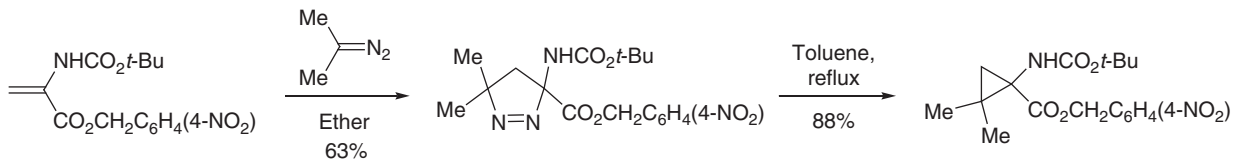
The thermal decomposition of pyrazolines has been used quite extensively in the past few decades to generate cyclopropane amino acids. The cycloaddition reaction of dehydroalanine with α,α-disubstituted diazo reagents proceeded smoothly to generate the corresponding pyrazoline (Scheme 3).[2] Nitrogen extrusion by pyrolysis afforded the corresponding cyclopropane in excellent yield.

Photolysis can also be used to decompose pyrazolines. For example, the 1,3-dipolar cycloaddition of a nucleoside derivative afforded a mixture of spiropyrazolines on treatment with diazomethane (Scheme 4).[3] A subsequent photochemically induced nitrogen extrusion reaction of the pyrazoline mixture provided excellent yield of the cyclopropane. This cyclopropanation procedure was found to be superior to those involving metal carbenes probably due to the highly functionalized nature and Lewis basicity of the starting material.

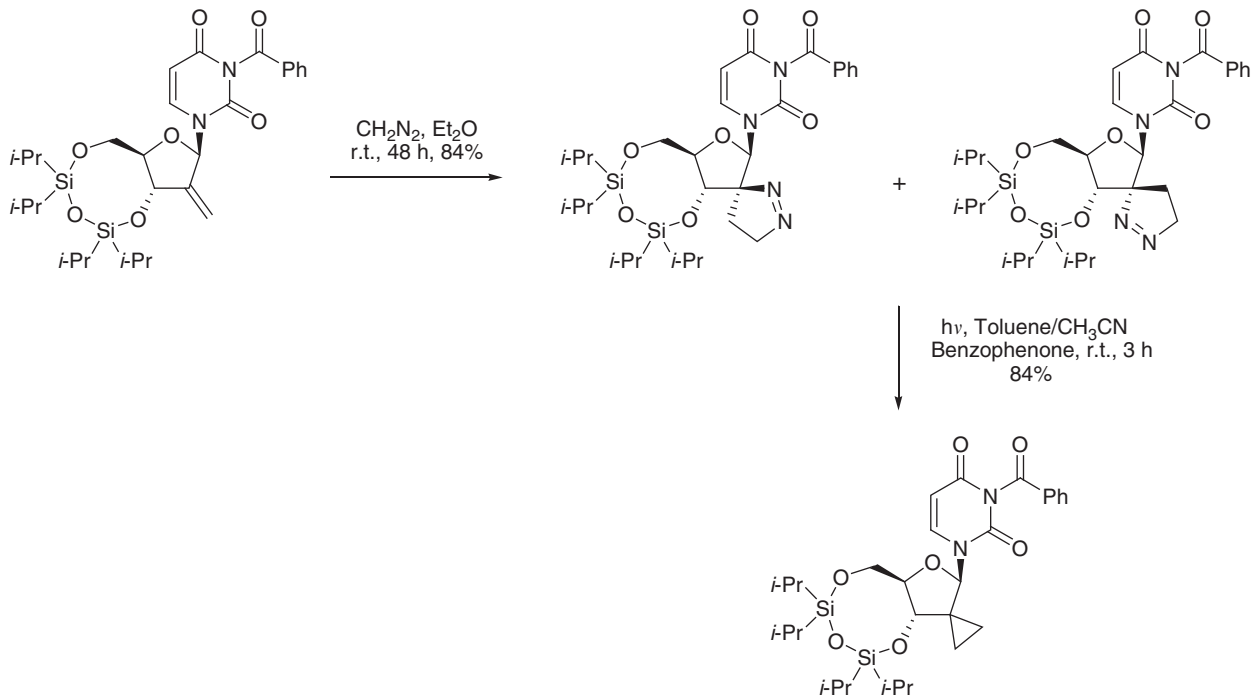
In some cases, Lewis acids can also be used to promote nitrogen extrusion from pyrazolines. Polysubstituted cyclopropane derivatives can be prepared in enantioenriched form by the [3+2] cycloaddition reactions of chiral 3-sulfinylfuranones. The dipolar cycloaddition led to either diastereomer when appropriate reaction conditions were employed (Scheme 5).[4] Thermal conditions to induce nitrogen extrusion led to cyclopropane ring opening products. A screening of Lewis acids indicated that ytterbium(III)triflate was optimal to promote this transformation (Scheme 6).[5]



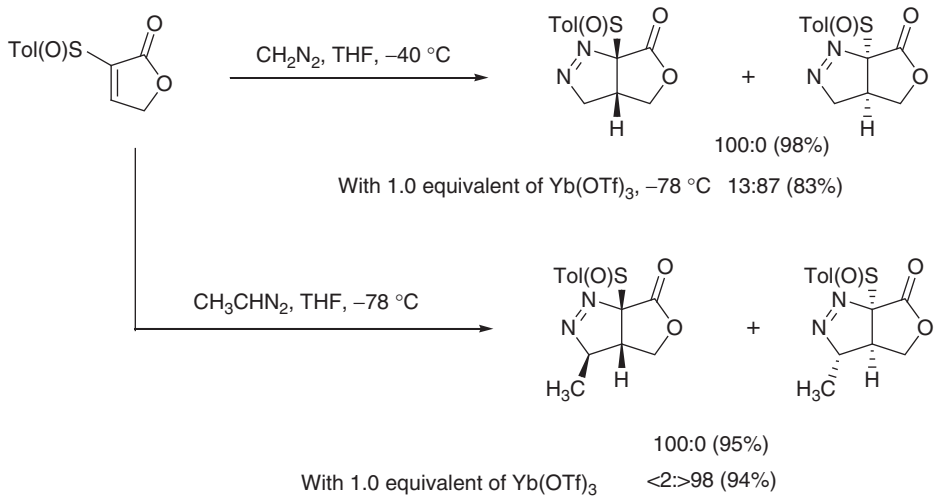
Scheme 2



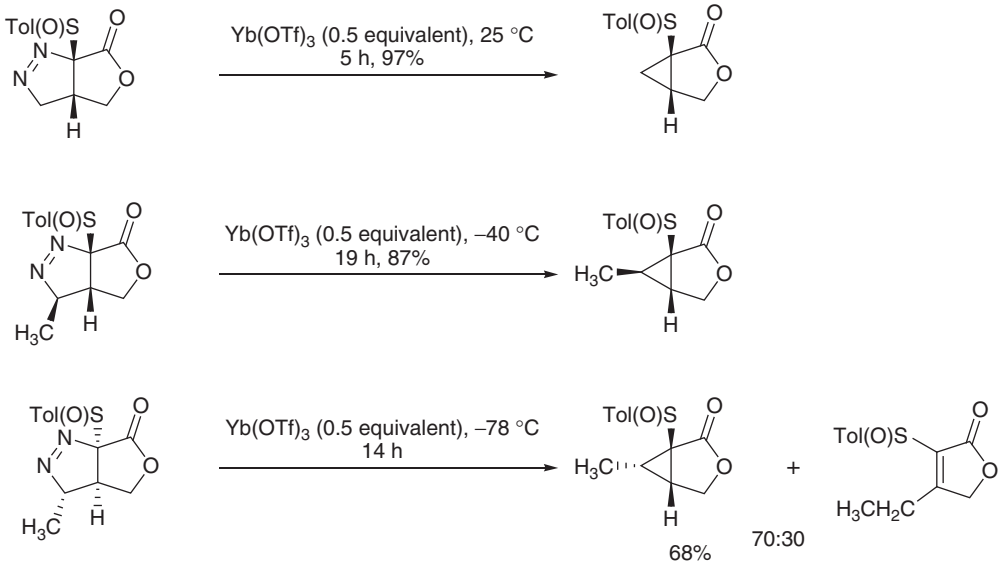
Scheme 3



Scheme 4



Scheme 5



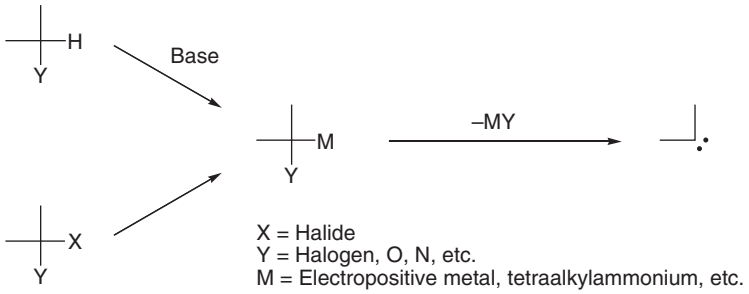
Scheme 6

4.19.3 Cyclopropanation with Lithium-derived Carbenes Prepared by α-Elimination

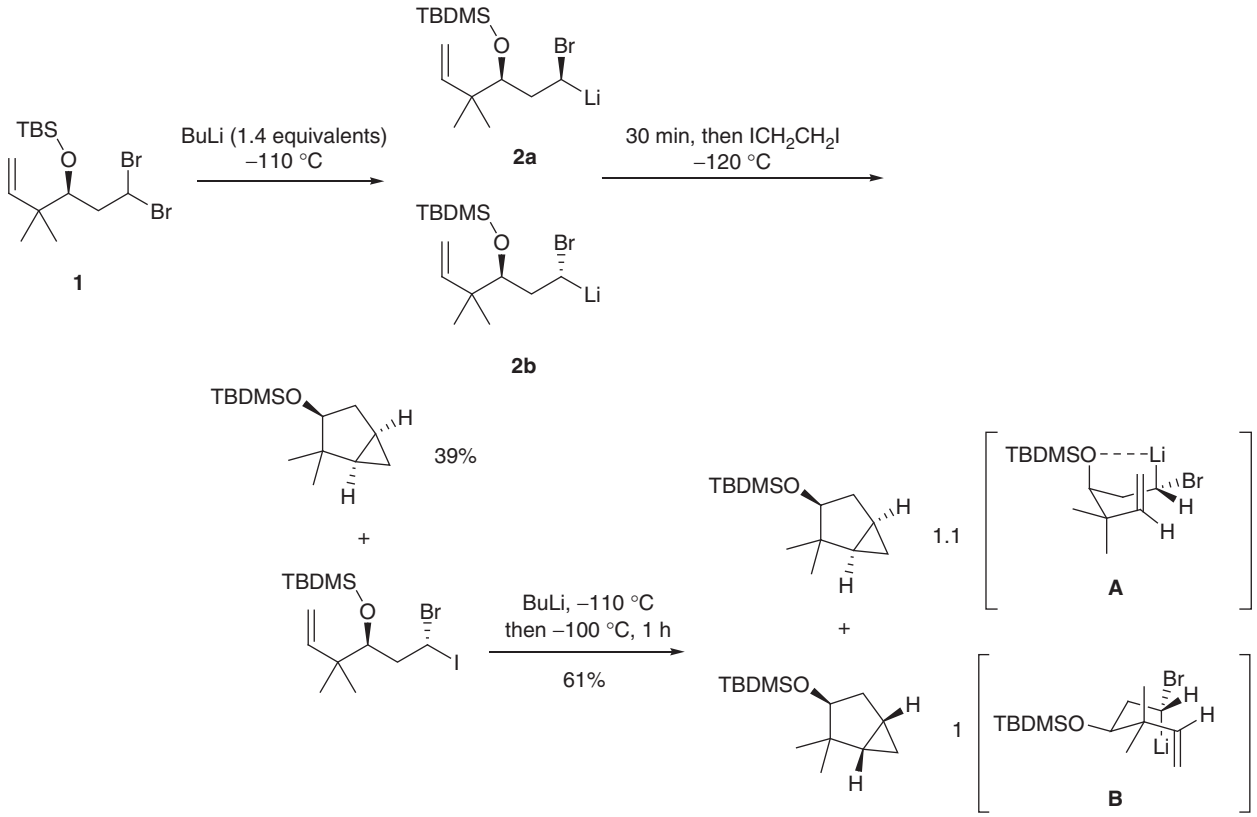
Generation of an organometallic species that bears a leaving group on the α-carbon can lead to a carbene (Scheme 7).

The stereochemical outcome of the intramolecular cyclopropanation of a chiral lithium carbenoid generated from a dihaloalkane was studied (Scheme 8).[6] It was shown that **2a** underwent a clean and rapid intramolecular cyclopropanation to give a single cyclopropane product, whereas its diastereomer was left unreacted at −120 °C. **2b** could be trapped with an electrophilic source of iodine. A subsequent regeneration of the lesser unreactive diastereomerically pure lithium carbenoid **2b** was accomplished and warming the reaction mixture to −100 °C induced the formation of a mixture of cyclopropane products (which results either from equilibration of both carbenoids **2a** and **2b** or via different mechanisms). Complex **A** was invoked to explain the reaction of **2a**, whereas **B** was proposed for the formation of the other diastereomericbicyclo[3.1.0] derivative.

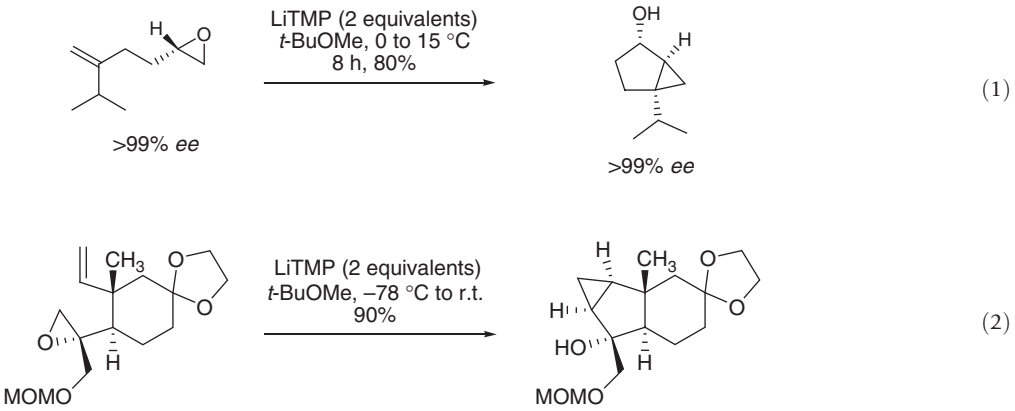
It is also possible to generate lithium carbenoid from epoxide. Treatment of an unsaturated terminal epoxide with a strong base generated an α-lithiated epoxide that underwent a highly diastereoselective intramolecular cyclopropanation (equations 1–2).[7,8] It is proposed that the diastereoselectivity arises from an initial *trans*-lithiation of the epoxide. Although these species are prone to undergo rapid carbene formation, it is postulated that the reaction occurs via the lithium carbenoid species. The diastereoselectivity complements that observed in the cyclopropanation reaction of cycloalkenol using zinc or samarium carbenoids.



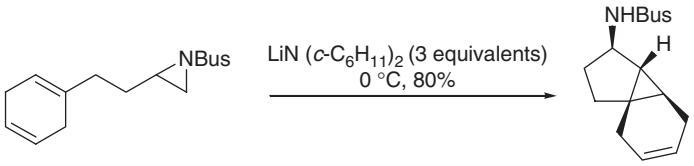
Scheme 7



Scheme 8



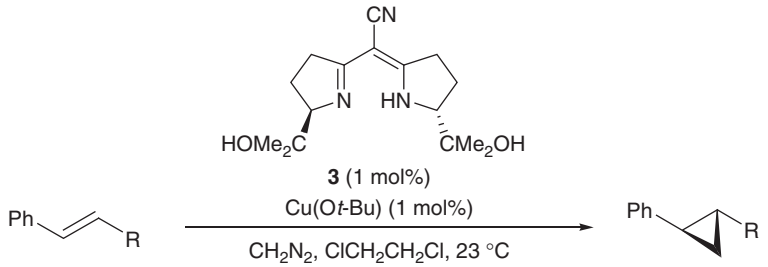
N-tert-Butylsulfonyl-protected (*N*-Bus) aziridines react in a similar fashion on treatment with lithium dicyclohexylamide to produce trans-aminobicycle[3.1.0]hexanes in good-to-excellent yields (equation 3).[9]



(3)

4.19.4 Cyclopropanation with Metal Carbenes Derived from Diazomethane

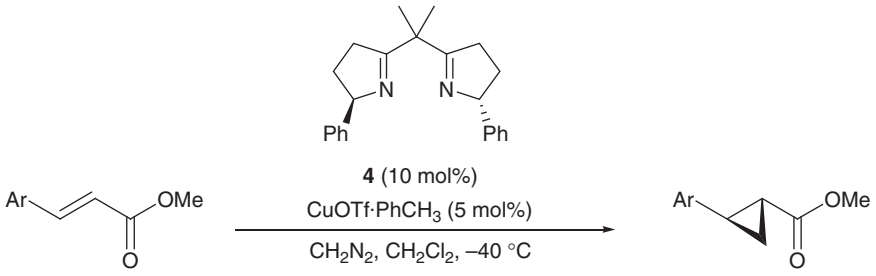
Many transition metal complexes can efficiently decompose diazomethane to produce metal carbenes.[10] Among these, palladium and copper salts have been the most widely used. Palladium complexes are particularly useful for the preparation of racemic cyclopropane derivatives; however, chiral versions do not lead to any enantioselectivities.[11] Conversely, moderate levels of enantioselectivities have been obtained using chiral copper complexes. Although the scope of these reactions is quite limited, a copper complex derived from chiral semicorrin ligand **3** is effective at converting 1-phenylpropene and methyl *trans*-cinnamate to their corresponding cyclopropane derivatives in modest yields and moderate enantioselectivities (equation 4).[12]



R = Me 75% *ee* (46%)
R = CO_2Me 70% *ee* (25%)

(4)

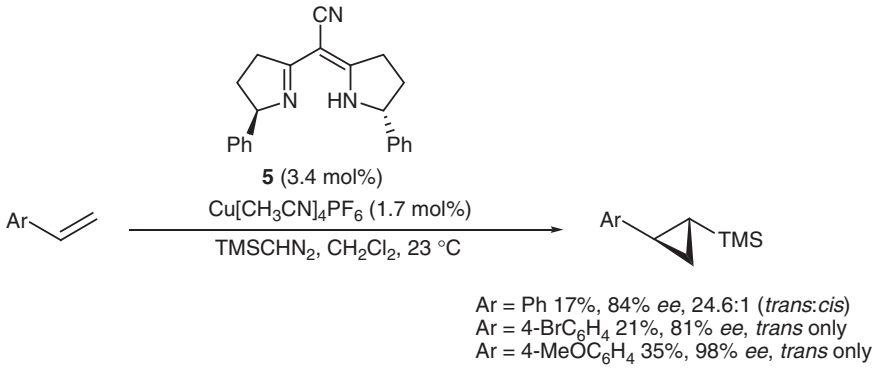
The cyclopropanation of *trans*-cinnamate esters using diazomethane and the copper complex derived from bisoxazoline4 proceeded in moderate-to-good yield, with enantiomeric excesses ranging from 55% to 80% (equation 5).[13]



Ar = Ph 80%, 72% *ee*
Ar = 4-$MeOC_6H_4$ 81%, 55% *ee*
Ar = 4-$O_2NC_6H_4$ 62%, 80% *ee*

(5)

Trimethylsilyl diazomethane can also be used as a diazomethane surrogate for this transformation, leading preferentially to the *trans*-cyclopropane isomer (equation 6).[14] Unfortunately, the chiral complex yielding the highest enantioselectivities produced the lowest yields. It should be pointed out that trimethylsilyl diazomethane was used as the limiting reagent in this methodology.

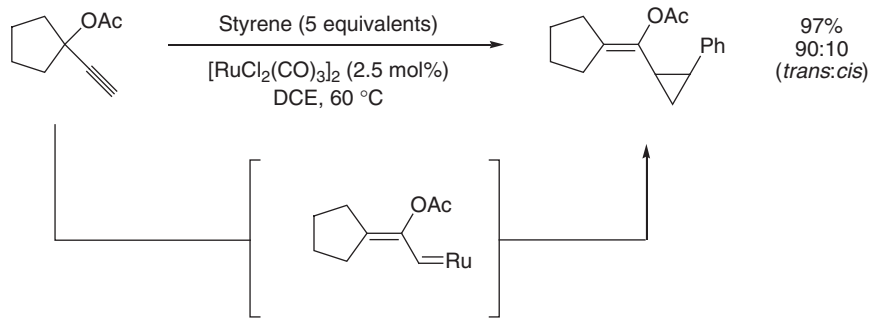


(6)

4.19.5 Cyclopropanation with Carbenes Derived from other Precursors

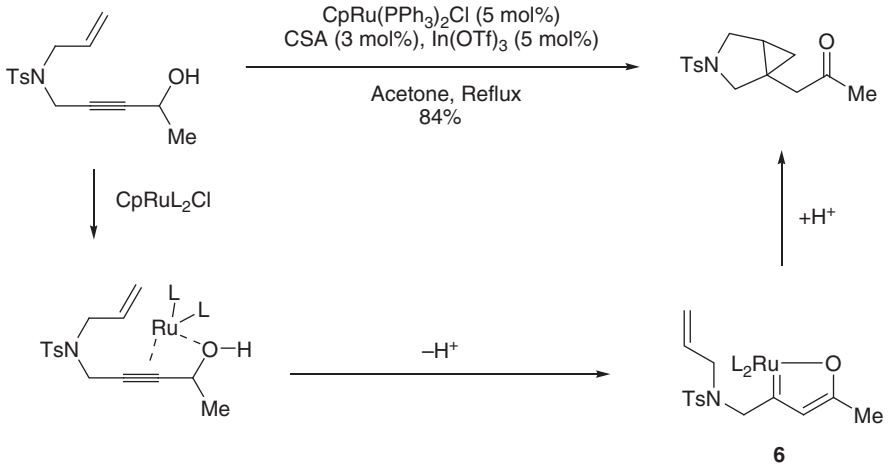
4.19.5.1 Metal Carbenes Derived from Alkynes

Several transition metal complexes react with alkynes in the presence of a nucleophile to generate metal carbenes that react with alkenes to give cyclopropanes. For example, treatment of propargylic carboxylates with a ruthenium catalyst generates a vinyl ruthenium carbene that undergoes intramolecular cyclopropanation in the presence of styrene (Scheme 9).[15,16]



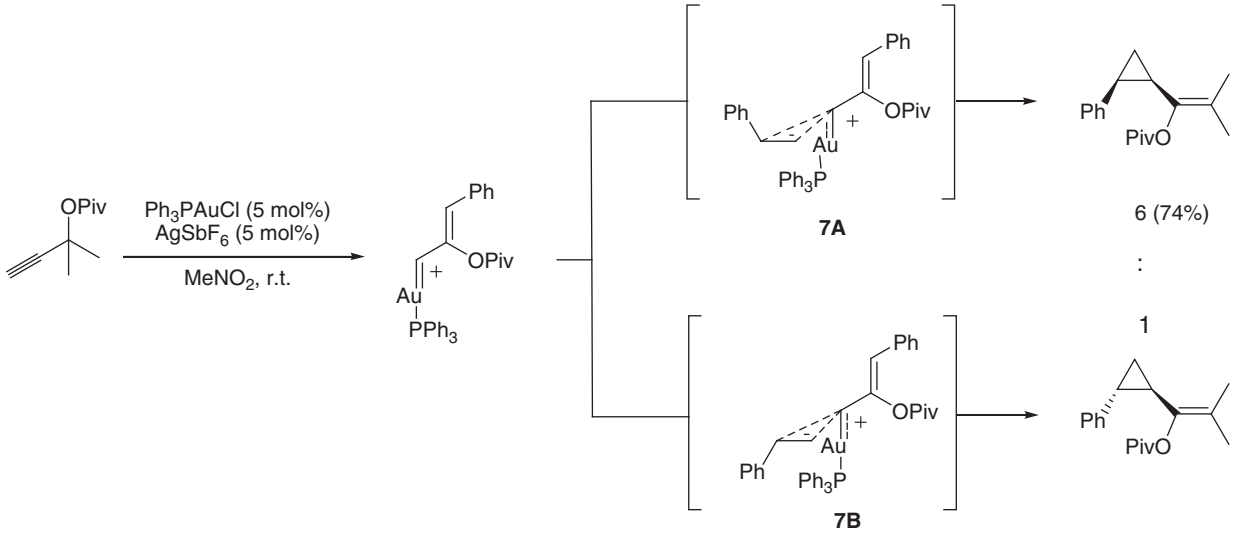
Scheme 9

It is also possible to access *β*-oxo ruthenium carbene from propargyl alcohols (Scheme 10). This method allows the preparation of [3.1.0]- and [4.1.0]-bicyclic skeletons if the carbenes are generated in the presence of an olefin.



Scheme 10

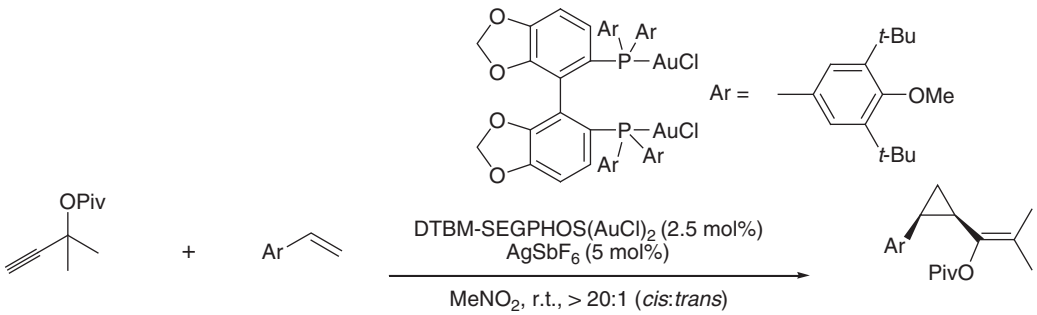
Gold(I) complexes effectively catalyze the cyclopropanation of olefins using propargylic esters.[17] The reaction proceeds through the formation of a gold(I) carbine intermediate from the propargylic ester followed by a *cis*-selective cyclopropanation (Scheme 11). The minimization of the steric interaction between the substituent on the alkene and the bulky phosphine ligand has been invoked to explain the diastereoselectivity of the reaction. The scope of the reaction is also quite broad with regard to the olefinic structure.



Scheme 11

An enantioselective version of the reaction using DTBM-SEGPHOS as chiral ligand has been reported (Table 1).[17]

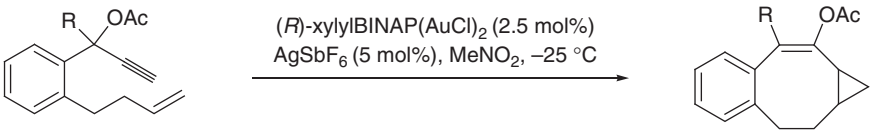
Table 1 Gold(I)-catalyzed enantioselective cyclopropanation of alkenes



Number	*Ar*	*Yield (%)*	ee *(%)*
1	Ph	70	81
2	2-MeC_6H_4	83	87
3	4-*t*-BuC_6H_4	82	81
4	2,6-Me-4-*t*-BuC_6H_2	71	94
5	2-BrC_6H_4	60	76
6	3-ClC_6H_4	69	76
7	4-FC_6H_4	85	82
8	1-Naphthyl	79	85

Gold(I)[18] and gold(III)[19] complexes are also effective at catalyzing an intramolecular version of this reaction. The enantioselective synthesis of 7- and 8-membered rings can be accomplished if the cyclopropanation is carried out in the presence of chiral gold complexes such as (R)-xylyl-BINAP$(AuCl)_2$, (R)-Difluorophos$(AuCl)_2$, or (R)-DTBM-Segphos$(AuCl)_2$ (Table 2).

Table 2 Enantioselective gold(I)-catalyzed intramolecular cyclopropanation



Number	*R*	*Yield (%)*	ee *(%)*
1	Me	94	92
2	Et	91	92
3	Allyl	98	90
4	$(CH_2)_2Ph$	80	90

4.19.6 Cyclopropanation with Carbenoid Reagents

4.19.6.1 Carbenoid Reagents in Cyclopropanation Reactions

Although the most commonly used carbenoid reagents for the conversion of alkenes into cyclopropane derivatives are zinc based, samarium and aluminum carbenoids are also suitable in the cyclopropanation of alkenes. The following subsections will describe the various reagents available and highlight their main differences in reactivity.

4.19.6.1.1 Zinc carbenoids

Many zinc carbenoid reagents have been prepared since the first reports by Emschwiller (**8**),[20] Wittig (**8**,**9**),[21,22] Simmons and Smith (**8**),[23] and Furukawa (**10**) (Figure 1).[24] They are synthesized by reacting diiodomethane with zinc/copper couple in diethyl ether or diethylzinc in a noncomplexing solvent,[24] using the appropriate stoichiometry. Treatment of zinc iodide with diazomethane in diethyl ether also produces the zinc carbenoid **8** or **9**, but this procedure has rarely been used in synthesis.[22]One of the main advantages of the Furukawa procedure is that it allows the use of noncomplexing solvents (such as dichloromethane and 1,2-dichloroethane) that are critical to improve the reactivity of the electrophilic reagent.

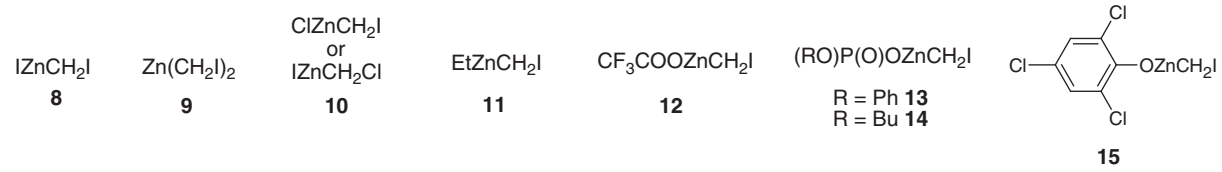
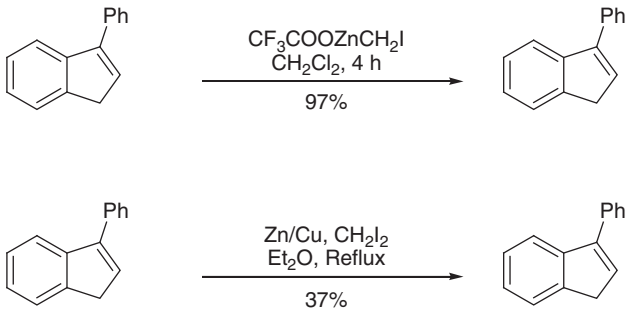


Figure 1

Since the Furukawa reagent (**10**) is not particularly stable, it has to be generated in the presence of the olefin to maximize the cyclopropanation yield due to its relatively rapid decomposition into propylzinc iodide. Replacement of diiodomethane with chloroiodomethane leads to reagent **10** that produces higher yields in some cyclopropanation reactions.[25] Several new zinc carbenoids have been added to the chemist toolbox to tailor their reactivities and properties to specific applications. Notable reagents include zinc trifluoroacetate **12**,[26,27] zinc phosphates **13** and **14**,[28,29] and zinc 2,4,6-trichlorophenoxide **15** (Figure 1).[30] Iodomethylzinc trifluoroacetate (**12**) shows considerable increased reactivity relative to the other zinc carbenoids, as demonstrated by the complete cyclopropanation of phenylindene within 3 h (Scheme 12).[26,31] Iodomethylzinc diphenyl and



Scheme 12

dibutylphosphate (**13** and **14**) are stable, less reactive, and they efficiently cyclopropanate electron-rich alkenes or those having proximal directing groups. Iodomethyl zinc 2,4,6-trichlorophenoxide (**15**) is relatively reactive, but the cyclopropanation reactions are usually limited to simple substrates.

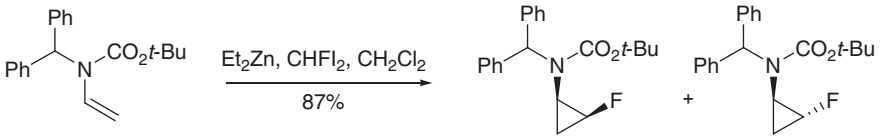
The structures of reagents **8**, **9**, **10**, and **13** in the solid state and in solution have been confirmed.[32,28]

Several α-substituted zinc carbenoids have been prepared from a suitable precursor and zinc metal or diethylzinc. **Table 3** illustrates the various possibilities. However, a mixture of diastereomers is usually observed when these reagents are used.

Table 3 Preparation of α-substituted zinc carbenoids

Number	*Starting material*	*Zinc reagent*	*Reagent*	*References*
1	$MeCHI_2$	Zn/Cu	MeCHIZnI	33
2		EtZnI	MeCHIZnI	34
3		Zn/Ag	MeCHIZnI	35
4		Et_2Zn	MeCHIZnEt	36
5	$MeCHBr_2$	Zn/Cu	MeCHBrZnBr	37
6	$TIPSOCH_2CH_2CHI_2$	Et_2Zn	$TIPSOCH_2CH_2CHIZnEt$	38
7	Me_2CBr_2	Zn (electrosynthesis)	$Me_2CBrZnBr$	39
8	Me_2CI_2	Et_2Zn	$Me_2CIZnEt$	40,41
9	$PhCHCl_2$	Zn (electrosynthesis)	PhCHClZnCl	39
10	$PhCHBr_2$	Zn (electrosynthesis)	PhCHBrZnBr	39
11	$PhCHI_2$	Et_2Zn	PhCHIZnI	36
12	CHI_3	Et_2Zn or EtZnI	$I_2CHZnEt(I)$	42,43
13	$CHBr_3$	Et_2Zn	$Br_2CHZnEt$	44
14	$CHCl_3$	Zn (electrosynthesis)	$Cl_2CHZnEt$	39
15	$CHBrCl_2$	Zn (electrosynthesis)	$Cl_2CHZnBr$	39
16	$CHBr_2Cl$	Zn (electrosynthesis)	ClBrCHZnBr	39
17	$CHFI_2$	Et_2Zn	FICHZnEt	45
18	$CHIF_2$	EtZnI	ICHFZnF	46
19	CF_2Br_2	Zn	$BrCF_2ZnBr$	47
20	$ArCHN_2$	ZnI_2	ArCHIZnI	48,49
21	CHI_3	Et_2Zn or EtZnI (2 equivalents)	$ICH(ZnI)_2$ or $ICH(ZnEt)_2$	43

In general, a mixture of diastereomers is usually observed when these reagents are used (equation 7).[45]



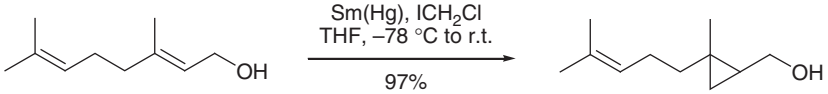
93:7

(7)

It is also possible to prepare α-alkyl, α-vinyl, α-aryl, α-alkoxy,[50] and α-amino zinc carbenoids[51] using an indirect strategy involving carbonyl precursors, zinc, and silyl chloride.

4.19.6.1.2 Samarium carbenoids

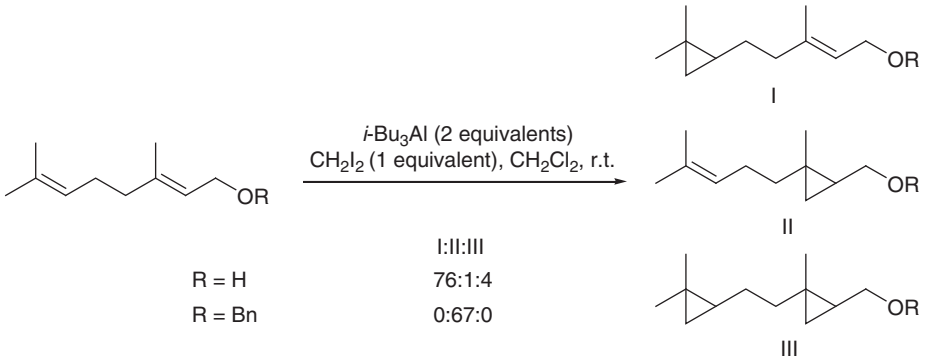
Samarium/mercury amalgamor samarium diiodide in conjunction with CH_2I_2 or ICH_2 Cl in tetrahydrofuran (THF) has been used to generate samarium carbenoids that are effective cyclopropanation reagents.[52] As with the zinc-based reagents, the samarium analogs react exclusively with allylic alcohols, and they can give good selectivities in alcohol-directed cyclopropanation reactions (equation 8).[53]



(8)

4.19.6.1.3 Aluminum carbenoids

Aluminum carbenoids display a unique reactivity that complements that of the zinc- and samarium-mediated cyclopropanation reaction.[54] The synthetic utility of these reagents is illustrated by the chemoselectivity observed in the cyclopropanation of geraniol that differs from that observed with zinc- and samarium-based reagents (equation 9). The observed chemoselectivity results from the protection of the oxygen lone pairs through the bulky aluminum alkoxide formation. The chemoselectivity is completely inverted (cyclopropanation occurs at the allylic ether olefin) if the alcohol is protected as a benzyl ether.[55]

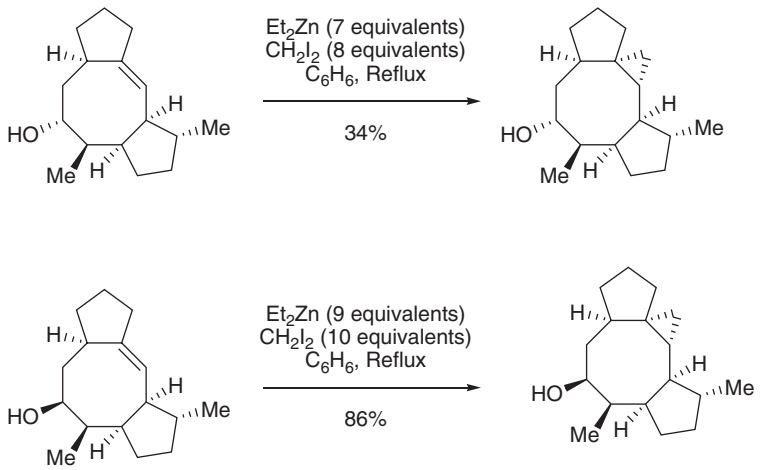


(9)

4.19.6.2 Diastereoselective Cyclopropanation of Chiral Alkenes

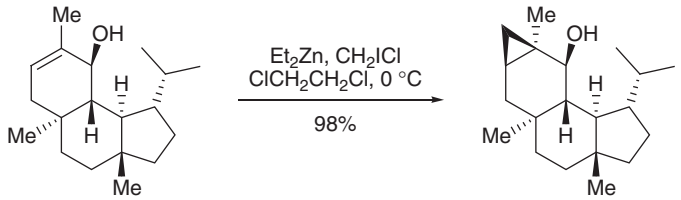
4.19.6.2.1 Reaction of chiral alkenes

The diastereoselective cyclopropanation of cyclic chiral alkenes that do not contain proximal Lewis basic groups can be highly diastereoselective if the two diastereotopic faces of the alkene are sterically differentiated (Scheme 13).[56] The reaction generally proceeds well and good diastereoselectivities are usually observed.



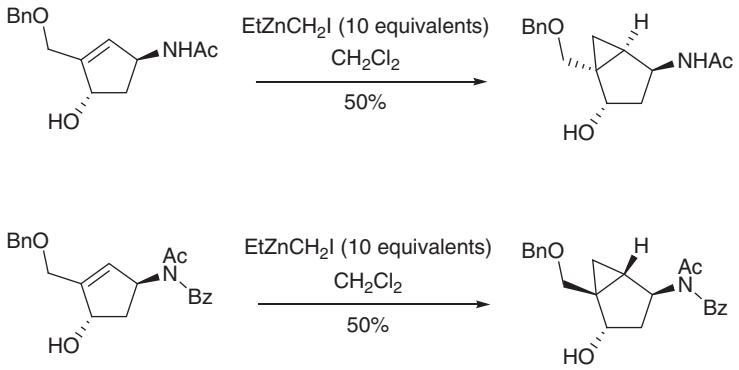
Scheme 13

Alternatively, not only can the presence of a proximal Lewis basic group direct the cyclopropanation reaction, but a more efficient reaction is observed (equation 10).[57] The spectacular effect of proximal basic groups has been exploited for several decades, and numerous examples were provided in the previous edition. In addition to alcohols (or zinc alkoxides), numerous examples illustrating the directing group ability of other Lewis basic groups such as benzyl ethers, tetrahydropyranyl ethers, methoxymethyl, benzyloxymethyl, (2-methoxyethoxy)methyl, amide carboxyl groups, amines,[58] and carbamates have been reported.



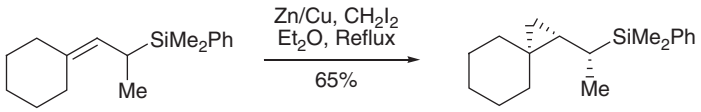
(10)

The cyclopropanation of functionalized cyclopentene derivatives shows that an NH-acyl group is a superior directing group to a zinc alkoxide when excess Furukawa reagent is used (Scheme 14).[59] However, the protection of the N–H leads to a reversal of the facial selectivity.



Scheme 14

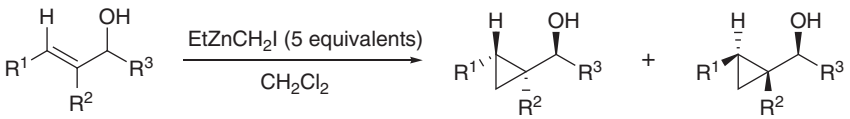
The cyclopropanation of chiral acyclic olefins is usually not highly diastereoselective unless a bulky substituent is present at the allylic position. For example, the cyclopropanation reaction of chiral allyl silanes is highly diastereoselective (equation 11).[60]



(11)

The *syn*-selective cyclopropanation of *Z*-substituted allylic alcohols using the Simmons–Smith reagent in diethyl ether is a well-established transformation that was extensively reviewed in the previous edition.[61] Samarium carbenoids are equally effective. Since then, it has been shown that excellent *syn*-selectivities are also observed with *E*-substituted allylic alcohols if an excess Furukawa reagent is used in dichloromethane (Table 4).[62] These conditions sharply contrast with those of the classical Simmons–Smith reaction (Zn/Cu, CH_2I_2, Et_2O) that produce an equimolar mixture of the two diastereomers.

Table 4 Diastereoselective cyclopropanation of chiral, acyclic allylic alcohols[62]



syn:*anti*

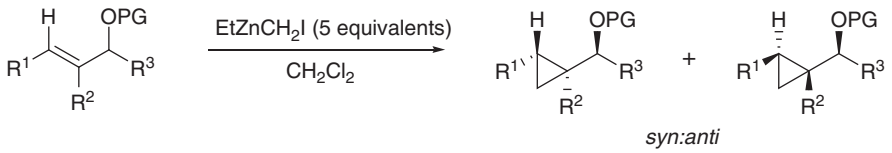
Number	R^1	R^2	R^3	*Yield (%)*	syn:anti
1	Me	H	Me	75	6:1
2	Ph	H	Me	86	7:1
3	Ph	H	Et	97	130:1
4	Pr	H	Et	87	110:1
5	Ph	H	*i*-Pr	97	>200:1
6	Ph	H	*t*-Bu	84	>200:1
7	Ph	Me	Me	95	33:1

Access to the *anti*-isomer is possible through the cyclopropanation reaction of silyl-protected *E*-substituted allylic alcohols (Table 5). The use of the more reactive Shi's reagent is necessary to maximize both the conversion and the *anti:syn* ratio.[63] Several less reactive zinc carbenoids led to lower conversions. *Z*-substituted allylic ethers lead to much lower diastereoselectivities.

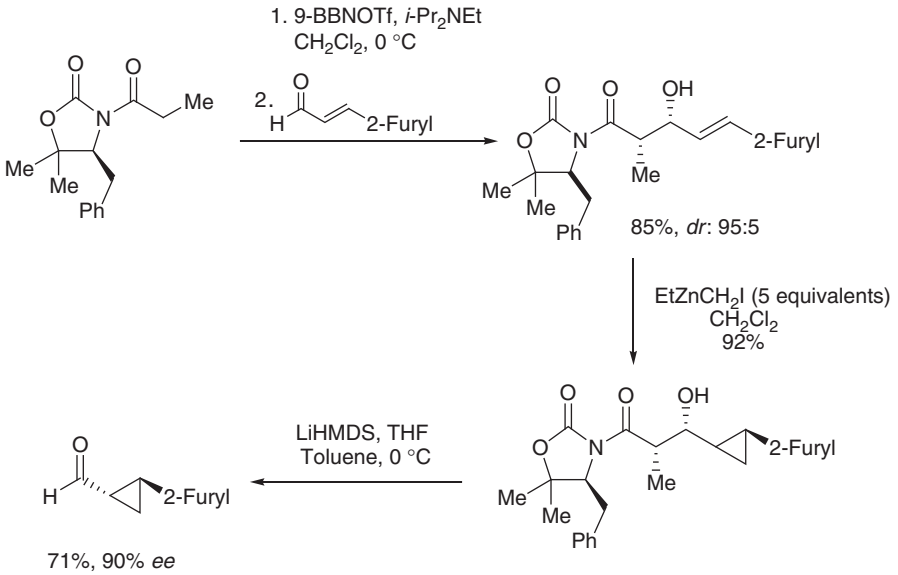
Several clever applications have relied on the diastereoselective cyclopropanation of chiral acyclic allylic alcohols to produce enantiomerically enriched cyclopropane derivatives. One example involves the *syn*-diastereoselective cyclopropanation of the *syn*-aldol product between (4*S*)-4-benzyl-5,5-dimethyl-3-propanoyl-1,3-oxazolidin-2-one and a variety of α,β-unsaturated aldehydes (Scheme 15).[64] A subsequent retro-aldol reaction with a strong base produces the corresponding cyclopropyl carboxaldehyde with high enantiomeric purity.

Several other clever extensions of this chemistry include combining a catalytic enantioselective alkylation or alkenylation of carbonyl groups with the diastereoselective cyclopropanation of the alkene.[65]The catalytic asymmetric dialkylzinc-mediated alkylation of an α,β-unsaturated aldehyde produces the corresponding allylicalkoxide (Scheme 16). This can undergo a diastereoselective cyclopropanation when treated with the reagent prepared from trifluoroethanol and diiodomethane. Alternatively, hydroboration of an alkyne followed by a boron/zinc transmetalation generates the vinylzinc species that undergoes a

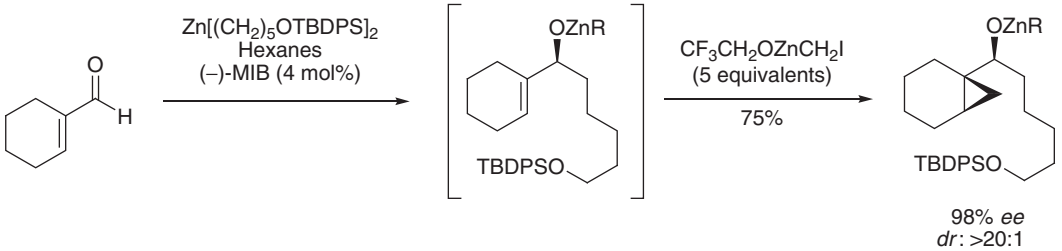
Table 5 *anti*-Selective cyclopropanation of chiral, acyclic allylic alcohols[63]



Number	*R^1*	*R^2*	*R^3*	*PG*	*Yield (%)*	anti:syn
1	Ph	H	Me	TBDMS	86	98:2
2	Ph	H	Me	TES	87	>99:1
3	Ph	H	Me	TIPS	88	>99:1
4	$PhCH_2CH_2$	H	Me	TIPS	84	96:4
5	Ph	H	Et	TBDMS	85	97:3
6	Ph	H	*i*-Pr	TES	87	97:3
7	Ph	H	Me	TIPS	88	98:2
8	Ph	Me	Me	TES	88	>99:1
9	Ph	Me	Et	TBDMS	88	99:1



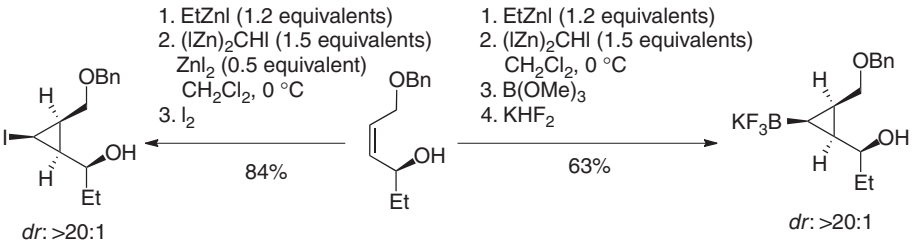
Scheme 15



Scheme 16

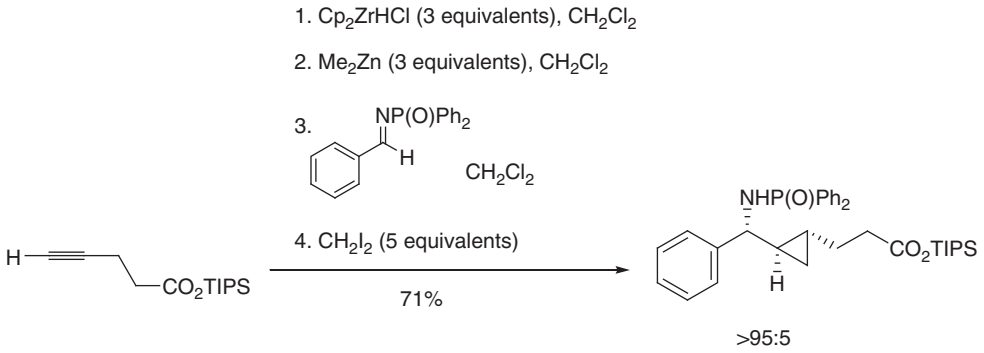
(2S)-(−)-3-*exo*-(morpholino)isoborneol-catalyzed addition to an aldehyde.[66,67] This addition proceeds with high enantiocontrol, and a subsequent diastereoselective cyclopropanation produces the *syn*-cyclopropylcarbinol. If the intermediate zinc alkoxide is quenched with tetramethylsilyl chloride (TMSCl) before addition of the cyclopropanation reagent, an *anti*-selective cyclopropanation occurs as shown in **Table 5**.[68]

The diastereoselective cyclopropanation of chiral allylic alcohols with *gem*-dizinc carbenoids proceeds with excellent diastereoselectivity (**Scheme 17**).[69] The corresponding cyclopropylzinc can be trapped with several electrophiles such as iodine or trimethylborate.[70] A subsequent cross-coupling reaction produces 1,2,3-substituted cyclopropane derivatives.



Scheme 17

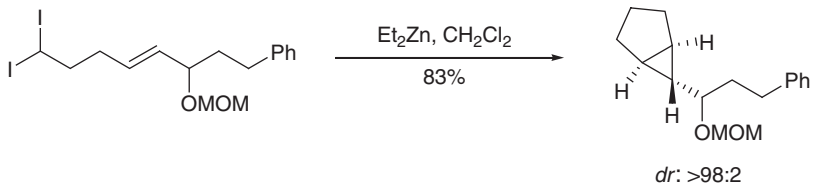
Chiral allylic amine prepared *in situ* by a tandem hydrozirconation/zirconium–zinc transmetalation/imine addition reacted on the addition of diiodomethane to produce the corresponding *anti*-cyclopropyl isomer with outstanding diastereocontrol (Scheme 18).[71,72]



Scheme 18

4.19.6.2.2 Diastereoselective intramolecular cyclopropanation

The synthesis of substituted bicyclo[n.1.0]alkenes has been shown to be possible via an intramolecular Simmons–Smith cyclopropanation.[73] The process involves a *gem*-diiodoalkane tethered allylic alcohol, which undergoes a diastereoselective cyclization on treatment with diethylzinc (equations 12–13). The protocol also provides access to bicyclo[4.1.0]heptanes.



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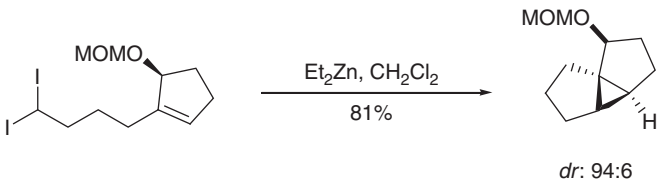
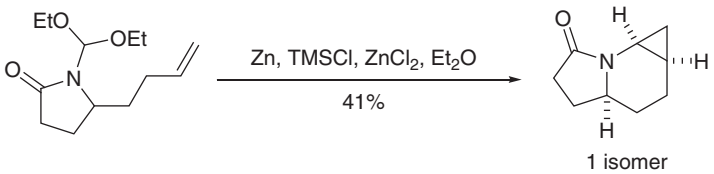


(13)

Another interesting intramolecular amido cyclopropanation reaction involves treating diethoxymethyl lactams with zinc and trimethyl silyl chloride (equation 14).[74] Modest yields yet excellent diastereocontrol are obtained with a preference for the formation of the *endo*-cyclopropane.



(14)

4.19.6.2.3 Chiral auxiliaries

Although these methods are not widely used today due to the effectiveness of reagent-based approaches (see Section 4.19.6.3), several covalently attached chiral auxiliaries are available to cyclopropanate various classes of alkenes. Substituted cyclopropyl methanol derivatives can be prepared using carbohydrate-derived chiral auxiliaries (Figure 2).[75–77] Although the transformations are highly diastereoselective, a large excess of the zinc reagent is necessary for high yields. A first equivalent is necessary to deprotonate the free hydroxy group, and the excess is a consequence of having numerous basic groups. Specific conditions have been developed to cleave the chiral auxiliary while preserving the cyclopropane ring.

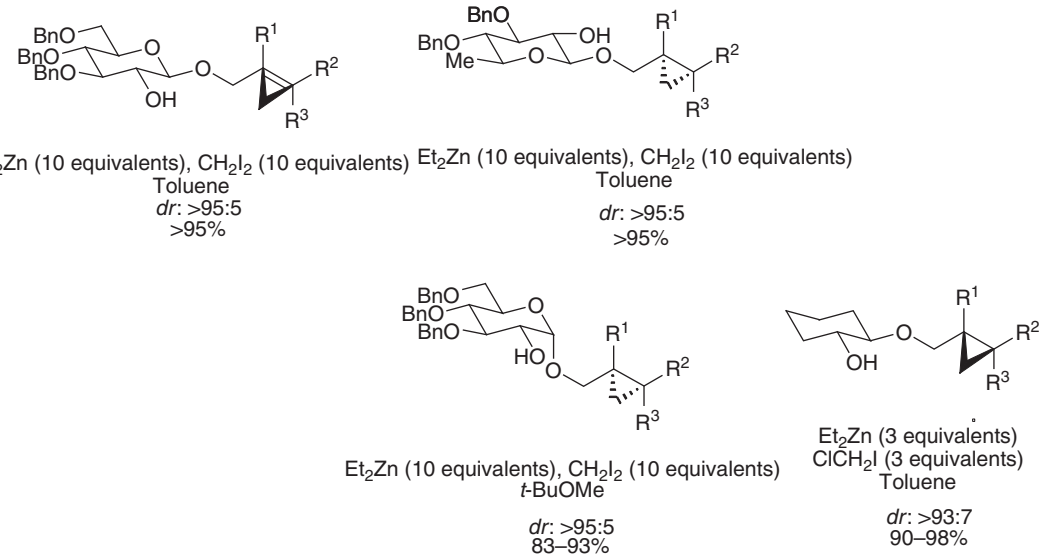


Figure 2

Inspired by the seminal work of Yamamoto[78,79] and Mash[80,81] (already reviewed in the previous edition), second-generation chiral acetals and ketals have also been developed for the enantioselective cyclopropanation of α,β-unsaturated carbonyl derivatives (Figure 3).[82–85]

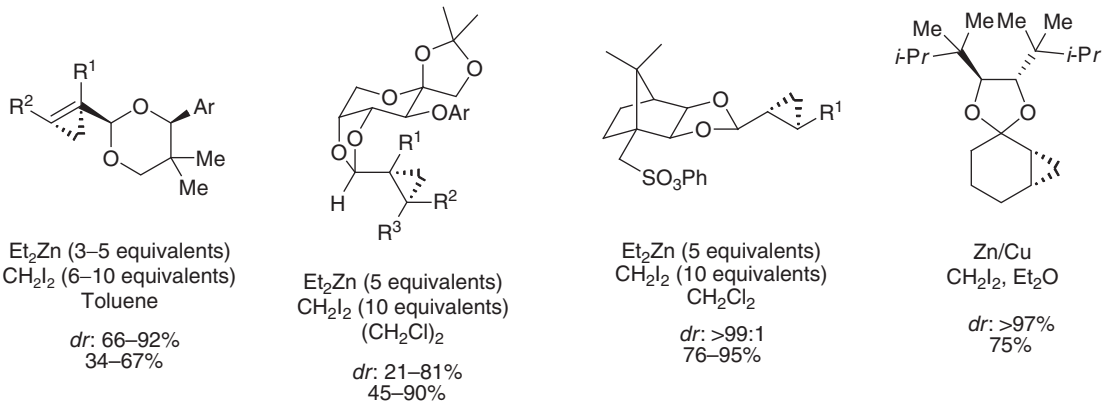
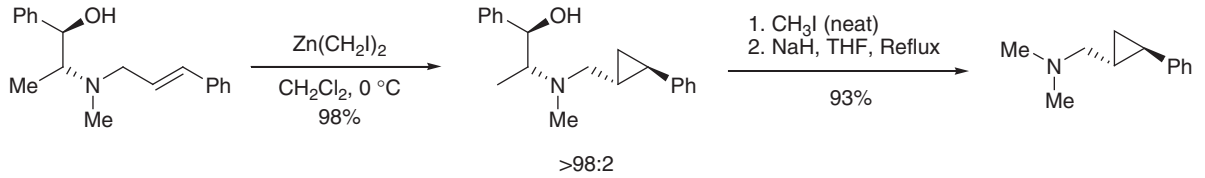


Figure 3

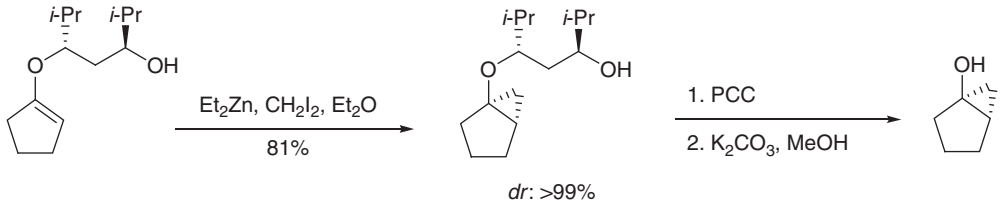
A chiral auxiliary-based approach has been reported for the preparation of chiral, nonracemic cyclopropyl methylamines. The cyclopropanation of allylic tertiary amines bearing a β-hydroxyl group occurred with high diastereoselectivity to generate the cyclopropyl methylamine (Scheme 19).[86] Cleavage of the auxiliary could be achieved on treatment with methyl iodide followed by heating. It should be stressed that the alcohol (or the intermediate zinc alkoxide) protects the basic nitrogen atom from being alkylated by the electrophilic zinc reagent. Tertiary amines are usually not compatible with the electrophilic zinc carbenoids.

A very useful class of chiral auxiliaries has been developed for the cyclopropanation of alkenes bearing heteroatoms. These auxiliaries allow for the preparation of enantiomerically enriched cyclopropanols, cyclopropyl amines, and cyclopropyl boronic acids. A method to generate substituted cyclopropanol derivatives using the cyclopropanation of a chiral enol ether derived from a



Scheme 19

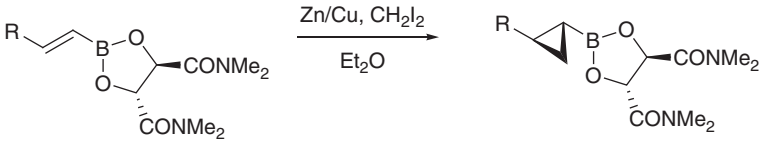
chiral 1,3-diol has been reported (Scheme 20).[87] The reaction displays high diastereocontrol with five- to eight-membered ring sizes, as well as with acyclic enol ethers.



Scheme 20

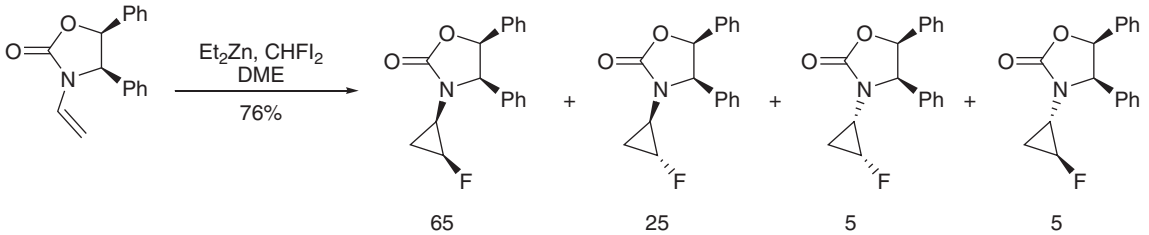
An alternate strategy to access cyclopropanol derivatives from an acyclic precursor has been reported (Table 6).[88] The hydroboration of an alkyne followed by treatment of the resulting boronic acid with tetramethyl tartramide produced the chiral alkene. A subsequent diastereofacial cyclopropanation afforded the corresponding cyclopropyl boronate ester, which could be oxidized to the cyclopropanol using hydrogen peroxide and potassium bicarbonate. Other chiral auxiliaries have been tested, such as those derived from $\alpha,\alpha,\alpha,\alpha$-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) ligands, but, in these cases, better diastereocontrol was achieved using palladium acetate/diazomethane[89] or using double differentiation with a chiral catalyst.

Table 6 Cyclopropanation of vinyl boronate esters



Number	*R*	*Yield (%)*	*Diastereomeric ratio*
1	*n*-Bu	67	97:3
2	Bn	61	94.5:5.5
3	Ph	46	95.5:4.5

The fluoro cyclopropanation of a chiral enamide has been studied for the preparation of fluoro-substituted cyclopropyl amines. The reaction produced a mixture of all four possible stereoisomers in which one of the *cis*-isomer was the major diastereomer formed (equation 15).[90]



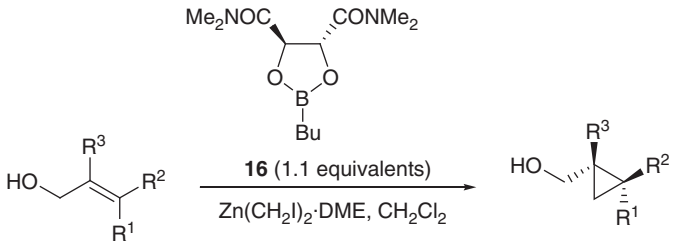
(15)

4.19.6.3 Enantioselective Cyclopropanation of Alkenes using Stoichiometric Additives

The enantioselective cyclopropanation reactions involving the use of stoichiometric chiral additives can be divided into two classes based on whether or not there is preassociation between the substrate and the chiral Lewis acid. The first class involves the enantioselective cyclopropanation of allylic alcohols, whereby a preassociation between the corresponding zinc alkoxide and the Lewis acidic chiral ligand takes place. The second type involves the enantioselective cyclopropanation of alkenes where there is no preassociation between the reagent and the alkene through a zinc alkoxide. The latter methodologies are referred to as enantioselective cyclopropanation reactions of unfunctionalized alkenes and are much more challenging when zinc carbenoids are used as reagents.

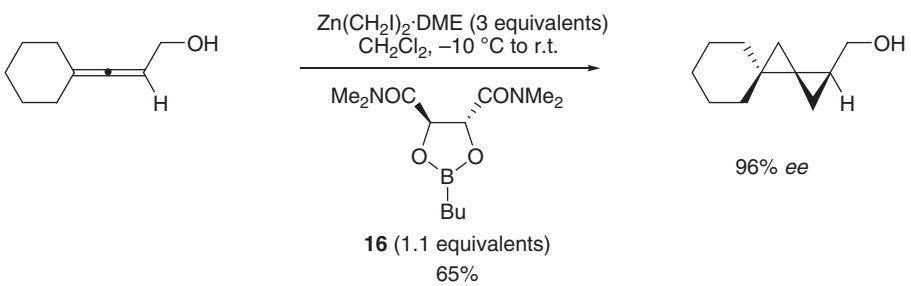
The cyclopropanation of allylic alcohols using stoichiometric chiral Lewis acid additives remains one of the most effective ways to generate enantiomerically enriched cyclopropyl methanol derivatives. The chiral dioxaborolane ligand **16**, prepared from tetramethyl tartramide and butyl boronic acid, is a chiral additive that has been extensively used since it was initially reported in allylic alcohol-directed cyclopropanation reactions (Table 7).[91,92]

Table 7 Enantioselective cyclopropanation of allylic alcohols



Number	*R*^{1}	*R*^{2}	*R*^{3}	*Yield (%)*	ee *(%)*
1	H	Ph	H	95	94
2	H	3-MeOC$_6$H$_4$	H	>98	93
3	H	Pr	H	80	93
4	H	PhCH$_2$CH$_2$	H	90	94
5	H	Bu$_3$Sn	H	88	90
6	H	I	H	83	90
7	Bu$_3$Sn	H	H	73	90
8	I	H	H	71	83
9	Et	H	H	90	93
10	BnOCH$_2$	H	H	92	91
11	Me	Me	H	85	94
12	H	Ph	Me	80	82
13	H	Et	CH$_2$OTIPS	>98	89
14	Me	Me	CH$_2$OTIPS	85	88

The reaction is efficient with a wide range of substituted allylic alcohols, including those containing *trans-*, *cis-*, *tri-*, and tetrasubstituted alkenes.[93] It is also possible to cyclopropanate allenes (equation 16)[94] and polyenes (equation 17)[95] with excellent enantiocontrol. This reaction has been applied for the elaboration of cyclopropane units of several natural products.



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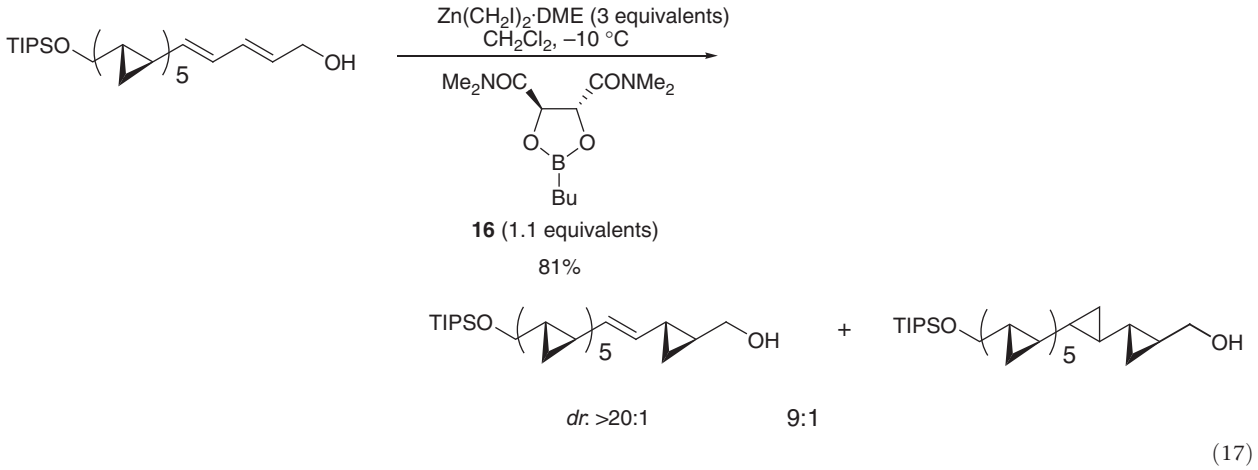
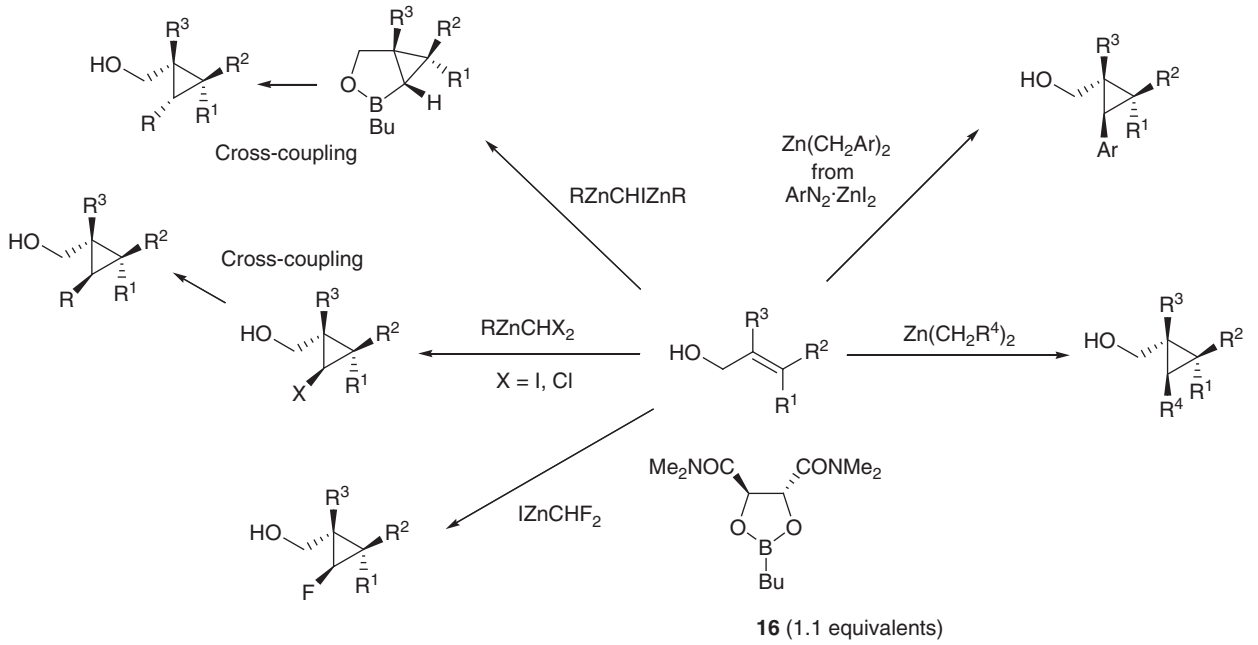


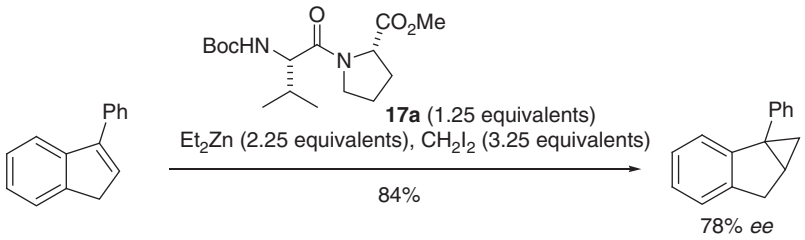
(17)

Ligand **16** is also very effective for producing enantioenriched 1,2,3-substituted cyclopropyl carbinol derivatives. Several methods allowing excellent diastereo- and enantioselectivities have been recently developed to access alkyl-,[38] aryl,[49] iodo-, chloro,[96] and fluoro[46]-substituted 1,2,3-substituted cyclopropanes (Scheme 21). Not only are the enantio- and diastereoselectivities usually very high for a wide range of substituted allylic alcohols, but access to all the possible diastereomers is sometimes possible. For example, any of the isomers of a cyclopropyl methanol derivative can be obtained selectively by selecting the appropriate starting allylic alcohol isomer and by carrying the zincocyclopropanation leading either to a cyclopropyl borinate or to the iodocyclopropanation. Both products can then be further derivatized by a transition metal cross-coupling reaction.



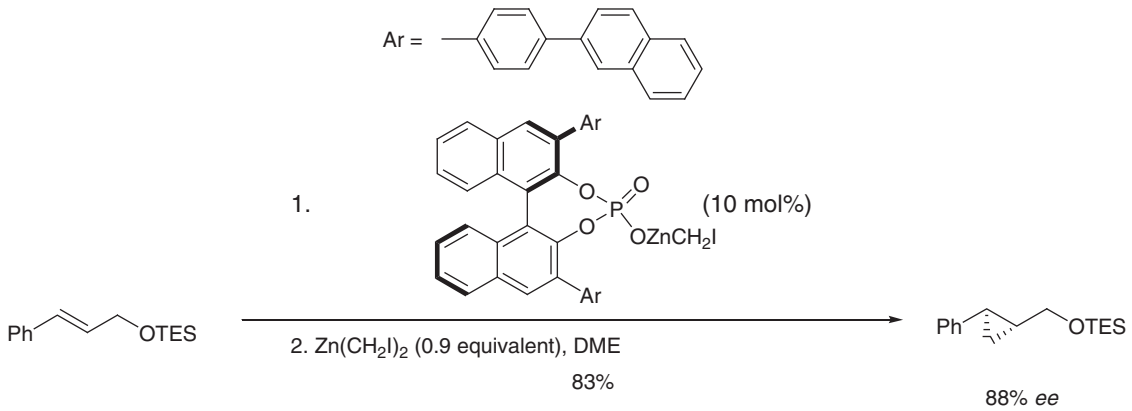
Scheme 21

All of the above methodologies rely on the use of either allylic alcohols or homoallylic alcohols as starting materials. They are not applicable to unfunctionalized alkenes. It was recently reported that the simple dipeptide **17a** derived from valine and proline could be used as a chiral additive in these reactions (equation 18).[97] Stoichiometric amounts of peptide **17a** can convert a variety of aryl-substituted alkenes to the corresponding cyclopropane with good-to-excellent enantioselectivities. The scope of the reaction will be discussed in the following section, as this ligand can be used in catalytic amounts under slightly modified reaction protocol.



(18)

An alternative approach involving a chiral iodomethylzinc phosphate derived from 3,3′-disubstituted binol was also reported for the cyclopropanation of a specific class of unfunctionalized alkenes.[28] It is also possible to obtain similar enantioselectivities with a catalytic amount of the chiral phosphoric acid by slightly changing the reaction conditions, but the reaction scope is very limited (equation 19).



(19)

4.19.6.4 Catalytic Asymmetric Cyclopropanation of Alkenes

The development of a catalytic asymmetric cyclopropanation reaction involving zinc carbenoids is challenging and the methods available have not been widely used in synthesis thus far. One reason for the lack of success is that the uncatalyzed background cyclopropanation reaction between an achiral haloalkylzinc reagent and an alkene is typically a rapid process. The notion of using Lewis acids to accelerate the cyclopropanation of alkenes has been contemplated and tested for several decades. The first groundbreaking work indicated that the addition of 0.12 equivalent of chiral disulfonamide ligand **18** led to the formation of the cyclopropanated product derived from cinnamyl alcohol in 76% enantiomeric excess.[98,99] This system was fully optimized, and bis(sulfonamide) **18** produced up to 89% ee for the cyclopropanation of cinnamyl alcohol (Table 8).[100] Substrates bearing both aliphatic and aromatic substitutions at either or both 3-positions of the allylic alcohol are suitable substrates. Conversely, substitution at the 2-position is not tolerated.

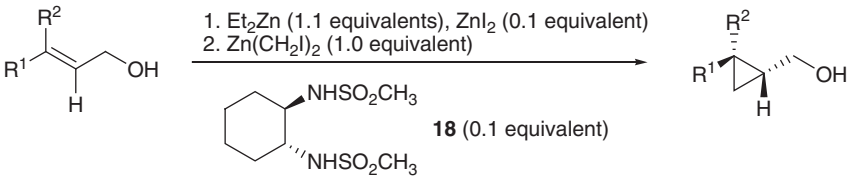
Alternatively, several other catalysts such as a titanium taddolate **19**[101] and a chiral aluminum **20**[102] have been shown to be very effective for the cyclopropanation of allylic alcohols, but the scope of the reactions is rather limited (Figure 4).

The dipeptide ligand **17a** is the most efficient available system for the catalytic asymmetric Simmons–Smith cyclopropanation of unfunctionalized alkenes.[103,104] Aryl-substituted cyclic olefins and silylenol ether are particularly good substrates for the reaction. The reaction must be carried out in the presence of a Lewis basic bidentate additive (ethyl methoxyacetate) to suppress the uncatalyzed cyclopropanation reaction that would lower the enantiomeric excesses of the products (Scheme 22).

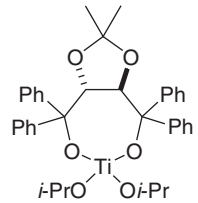
4.19.7 Michael-Induced Ring Closure Reactions

The conjugated addition reaction of a nucleophile to an α,β-unsaturated olefin bearing an electron-withdrawing substituent and a γ-leaving group is another convenient method to prepare cyclopropanes (see Scheme 1).[105,106] These reactions are called either 'Michael-initiated' or 'Michael-induced ring-closure.' As discussed in the first edition (Chapter 4.6 Methylene and Non-functionalized Alkylidene Transfer to Form Cyclopropanes), although many ylides have been used (phosphorus, tellurium, arsenic, etc.), sulfur ylides, such as in the Corey–Chaykovsky cyclopropanation, are the most commonly employed nucleophiles for the addition of unfunctionalized methylene units to alkenes (Figure 5).

Table 8 Catalytic asymmetric cyclopropanation of allylic alcohols with bis(sulfonamide) 18



Number	R^1	R^2	*Yield (%)*	ee *(%)*
1	Ph	H	92	89
2	$PhCH_2CH_2$	H	88	89
3	H	Ph	81	81
4	H	$PhCH_2CH_2$	93	72
5	Ph	Me	92	89
6	Me	$PhCH_2CH_2$	89	82



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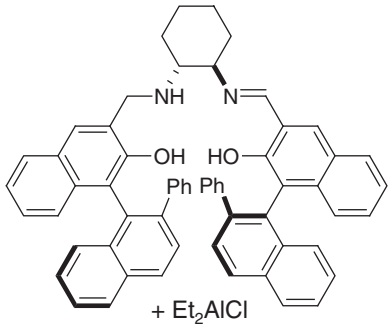

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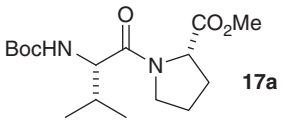
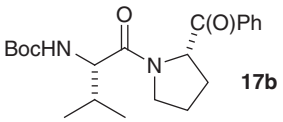


17a

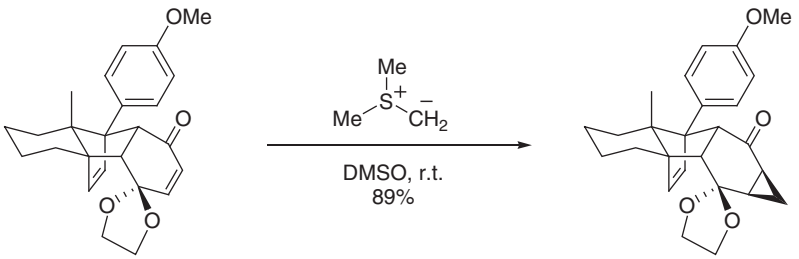


17b

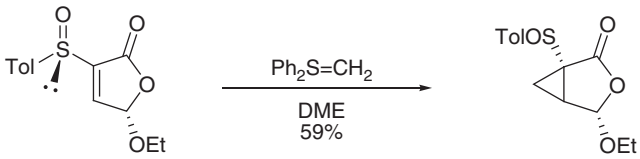
Figure 4

4.19.7.1 Diastereoselective Michael-induced Ring Closure Reactions

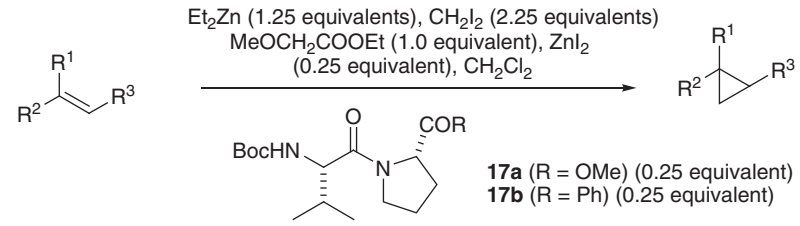
The level of selectivity of Michael-induced ring closure reactions on chiral cyclic alkenes is usually governed by steric interactions. Preferential attack of the nucleophile on the most sterically accessible face of the double bond is observed (equations 20 and 21).[107,108]

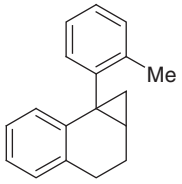


(20)

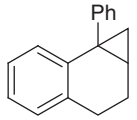


(21)

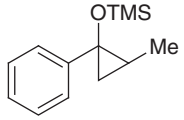




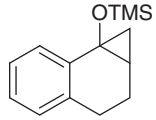
89% *ee* (60%)
(**17a**)



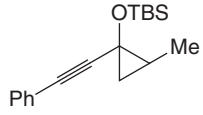
89% *ee* (87%)
(**17a**)



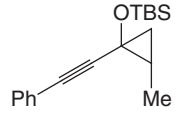
93% *ee* (99%)
(**17b**)



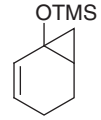
93% *ee* (97%)
(**17b**)



86% *ee* (89%)
(**17b**)



93% *ee* (91%)
(**17b**)



92% *ee* (79%)
(**17b**)

Scheme 22

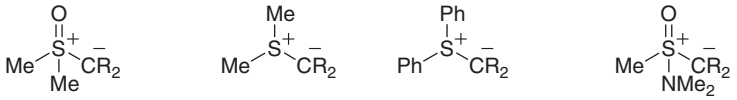
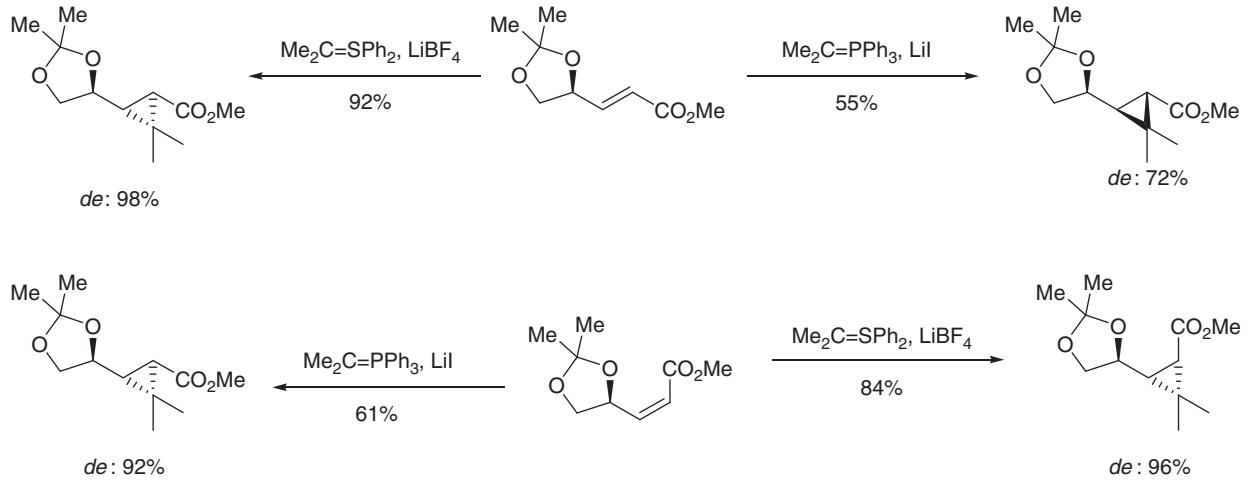


Figure 5

In the case of acyclic alkenes, diastereomeric mixtures are often obtained. The reaction is typically nonstereospecific with regard to the double bond geometry and the most thermodynamically stable *trans*-product is usually the major isomer observed. However, it is sometimes possible to obtain several of the potential isomers with good selectivity by modifying the nucleophile and the reaction conditions (Scheme 23).[109]

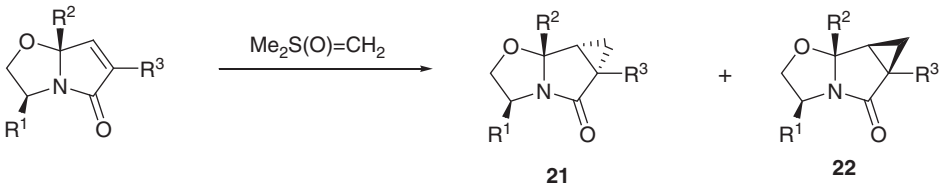


Scheme 23

4.19.7.2 Chiral Auxiliary-based Michael-induced Ring Closure Reactions

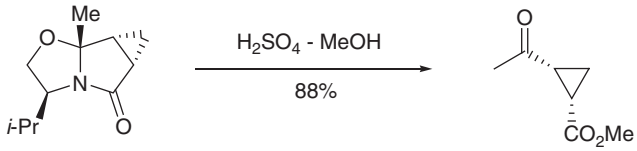
One of the first very efficient chiral auxiliaries for Michael-induced ring closure reaction that has been reported is based on the chiral bicyclic lactam framework (Table 9).[110] The diastereoselective cyclopropanation can be performed using sulfur ylides as well

Table 9 Diastereoselective cyclopropanation using chiral bicyclic lactam



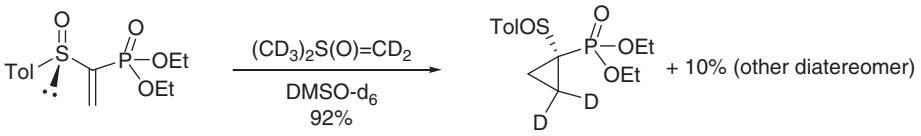
Number	R^1	R^2	R^3	*Yield (%)*	*Ratio (**21**:**22**)*
1	*i*-Pr	Me	H	64	40:1
2	*i*-Pr	Me	CO_2CH_3	65	100:1
3	*i*-Pr	Me	C_6H_5	60	>29:1
4	*i*-Pr	Me	$SOCH_3$	90	>19:1
5	*i*-Pr	Me	SO_2CH_3	70	>19:1
6	*t*-Bu	Me	H	81	19:1
7	*i*-Pr	H	$SOCH_3$	50	<1:19
8	*i*-Pr	H	CO_2CH_3	50	<1:30
9	*t*-Bu	H	H	40	<1:19

as a [2+3] cycloaddition–photolysis sequence. Hydrolysis of the auxiliary provides access to substituted cyclopropanes (equation 22).



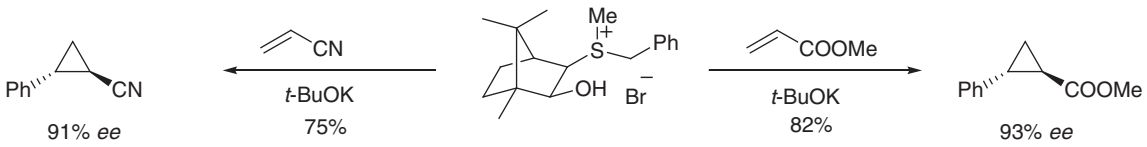
(22)

Chiral sulfoxides have also been used as acceptors. For example, the asymmetric cyclopropanation of vinyl *p*-tolyl sulfoxides react with unfunctionalized sulfur ylides in a highly diastereoselective fashion (equation 23).



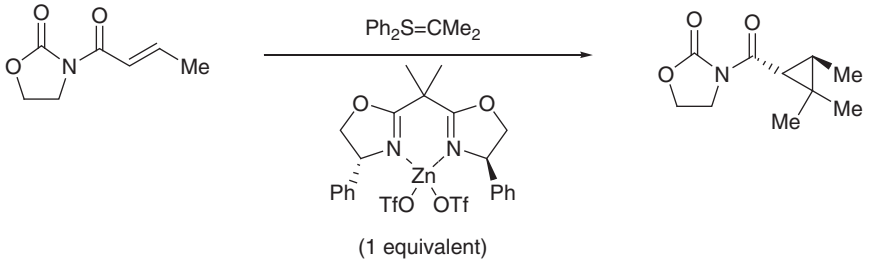
(23)

An alternative approach involves using chiral nucleophiles that undergo enantio- and diastereoselective cyclopropanation reactions of α,β-unsaturated carbonyl derivatives. For example, a camphor-derived sulfonium ylide adds to methyl acrylate or acrylonitrile to give the corresponding cyclopropanes with excellent selectivities and good yields (Scheme 24).[111]



Scheme 24

The reaction of *N*-enoyl oxazolidinones with diphenyl sulfonium isopropylide has been achieved with good enantiocontrol using a stoichiometric amount of zinc(II)·bis(oxazoline) complex (equation 24).[112]



(24)

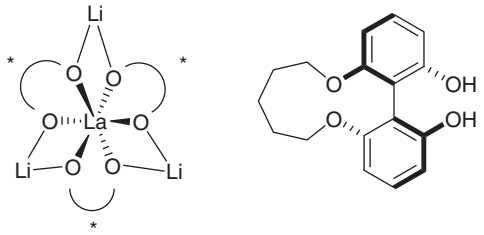
Many other methods provide access to substituted vinylcyclopropanes from vinyl-stabilized anions.[113]

4.19.7.3 Catalytic Asymmetric Michael-induced Ring Closure Reactions

Very few catalytic asymmetric Michael-induced ring closure reactions have been reported for the delivery of unfunctionalized methylene units into an unsaturated olefin. The asymmetric cyclopropanation of enones and an *N*-acylpyrrole with dimethyloxosulfonium methylide can be promoted by a La-Li3-(biphenyldiol)-NaI system (Figure 6 and Table 10).[114] The scope of the reaction is limited to β-aryl, β-heteroaryl, and β-styryl-unsaturated ketones, but a pyrrole ketone is a suitable substrate and it can be further functionalized (Scheme 25).

A catalytic method to prepare phenyl-substituted cyclopropane derivatives involves the *in situ* generation of a chiral sulfonium ylide from a rhodium carbene. The transformation initially starts with the generation of the diazo compound (from the sodium salt of tosyl hydrazone) that reacts with rhodium(II) acetate to generate the rhodium carbene (Table 11).[115] Subsequent alkylation of chiral thioether **23** leads to the sulfonium ylide that undergoes the Michael-induced ring closure process. Good enantio- and diastereoselectivities are observed.

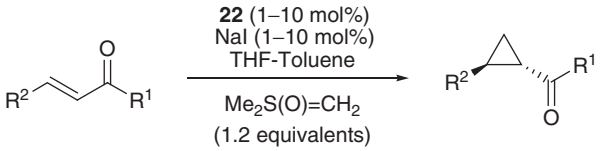
Several very useful asymmetric catalytic methods allow for the addition of carbonyl-stabilized ylides to generate polyfunctionalized cyclopropane derivatives[116] but these fall beyond the scope of this chapter.



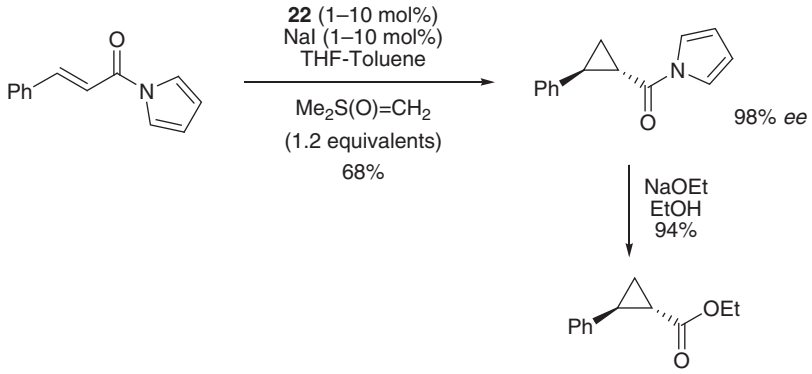
22

Figure 6

Table 10 Catalytic asymmetric cyclopropanation of enones



Number	R^1	R^2	*Yield (%)*	ee *(%)*
1	Ph	Ph	96	94
2	4-ClC_6H_4	Ph	93	93
3	4-$MeOC_6H_4$	Ph	95	97
4	Ph	4-ClC_6H_4	92	95
5	Ph	4-$MeOC_6H_4$	93	96
6	Ph	2-Furyl	96	99
7	Ph	2-Thienyl	94	99
8	Ph	4-Pyridyl	91	95
9	4-$AllylOC_6H_4$	Ph	92	96
10	Ph	–CH=CHPh	89	91
11	Me	Ph	74	84
12	*i*-Pr	Ph	73	94

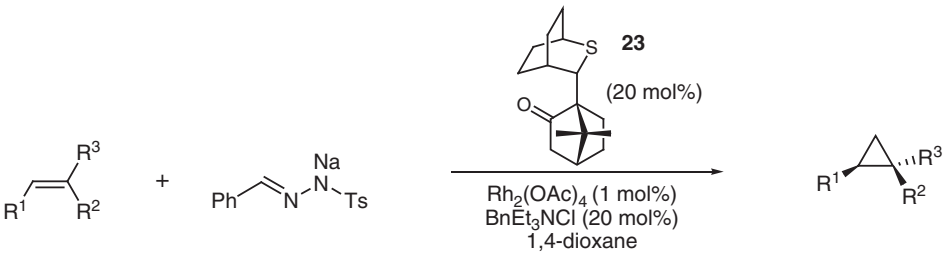


Scheme 25

4.19.8 Conclusion

As outlined in this chapter, several very useful methods have been developed in the past few decades for the enantioselective preparation of alkyl- and aryl-substituted cyclopropane derivatives from alkenes. Specific methods to convert either electron-rich (zinc carbenoids, gold carbenes) or electron-poor alkenes (cycloaddition or Michael-induced ring closures) into cyclopropanes have been reported. For example, the enantioselective cyclopropanation of allylic alcohols proceeds with good enantiocontrol with stoichiometric ligands whereas the catalytic version is quite substrate specific. More recently, access to diastereo- and enantioenriched functionalized cyclopropapane derivatives (halo-, borinate, etc.) that are amenable to further functionalization has become possible. However, all the possible diastereomers are not yet available in enantioenriched form using this approach. It is

Table 11 Catalytic asymmetric cyclopropanation of electron-deficient alkenes with chiral thioether 23



Number	R^1	R^2	R^3	*Yield (%)*	dr *(*trans:cis*)*	ee *(%)*
1	Ph	H	COPh	73	4:1	91
2	Me	H	COPh	50	4:1	90
3	H	*N*-succinimide	CO_2Et	55	1:7	91
4	H	$N(Boc)_2$	CO_2Me	72	1:6	92

anticipated that methods to provide access to these compounds will be the focus of research over the next few years. Significant advances have been made in the area of Michael-induced ring closure reactions using organocatalysis, but the most interesting discoveries involve the preparation of highly functionalized cyclopropane derivatives (not covered in this chapter). The field of asymmetric catalysis has also provided very useful methodologies, although truly general methods are still lacking. One interesting discovery is the use of gold carbenes as effective cyclopropanating intermediates that are conveniently prepared catalytically from alkynes. However, no general methodology is currently available for the enantioselective, catalytic methylene transfer to an unfunctionalized disubstituted alkene. Although important efforts have been invested into the use of diazomethane or Simmons–Smith type reagents, a scalable and practical methodology that produces a high level of enantioselection is still lacking.

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4.20 Addition of Ketocarbenes to Alkenes, Alkynes, and Aromatic Systems

JI García, L Salvatella, E Pires, JM Fraile, and JA Mayoral, Universidad de Zaragoza-CSIC, Calle Pedro Cerbuna, Zaragoza, Spain

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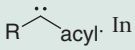
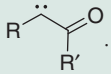
Glossary

Acyl carbene Any compound  . In organic chemistry, an unspecified acyl carbene is commonly a carboxylic acyl carbene.  . Synonyms: α-oxocarbene, ketocarbene.

Carbene The electrically neutral species H_2C or any of its derivatives, in which the carbon is covalently bonded to two univalent groups and bears two nonbonding electrons in spin-paired (singlet) or spin-nonpaired (triplet) states.

Carbenoid Complexed carbene-like entity that displays the reactivity characteristics of a carbene, either directly or by acting as a source of carbene.

Enantiomeric excess For a mixture of (+) and (−) enantiomers, with composition given as the mole or weight fractions F(+) and F(−), (where F(+)+F(−)=1) the enantiomer excess is defined as |F(+)−F(−)| (and the percent enantiomer excess by 100|F(+)−F(−)|). This term is abbreviated as *e.e.* or *ee*.

Metal–carbene complex Any metal complex of the type R_2CML_n (M=metal, L=ligand) in which formally a carbene is coordinated to a metal.

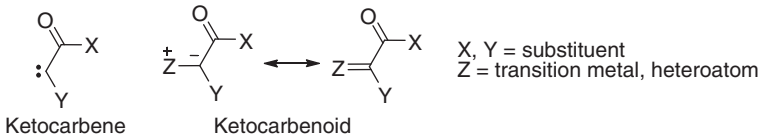
Sigmatropic rearrangement A molecular rearrangement that involves both the creation of a new σ-bond between atoms previously not directly linked and the breaking of an existing σ-bond. There is normally a concurrent relocation of π-bonds in the molecule concerned, but the total number of π- and σ-bonds does not change.

Stereoselectivity The preferential formation in a chemical reaction of one stereoisomer over another. When the stereoisomers are enantiomers, the phenomenon is called enantioselectivity; when they are diastereoisomers, it is called diastereoselectivity.

Ylide Compound in which an anionic site Y^- is attached directly to a heteroatom X^+ (usually nitrogen, phosphorus, or sulfur) carrying a formal positive charge: R–X^+–Y^-–R. If X is a saturated atom of an element from the first row of the periodic system, the ylide is commonly represented by a charge-separated form; if X is a second, third, etc., row element uncharged canonical forms are available: R–X=Y–R.

4.20.1 Introduction

Although ketocarbenes have been defined by the IUPAC as 'carbenes bearing an oxo function at an unspecified site,'[1] carbenes directly bound to a carbonylic functional group (aldehyde, ketone, ester, amide, etc.) will only be considered in this chapter. The high reactivity of ketocarbenes can be moderated for synthetic usefulness by means of electron density donation from a heteroatom (yielding an ylide)[2] or a transition metal (leading to a metal–carbene complex).[3] The resulting zwitterionic species (named as 'ketocarbenoids' in this chapter) can be stabilized in many cases by back donation from the occupied *p* orbital of the negatively charged carbon to a vacant orbital of the heteroatom or the transition metal.



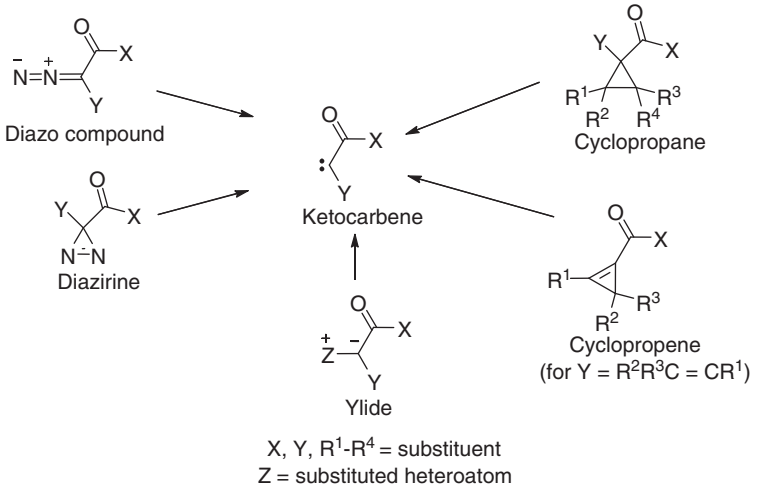
Since the preparation of the chapter 'Addition of Ketocarbenes to Alkenes, Alkynes, and Aromatic Systems' by Davies in early 1989 for the first edition of Comprehensive Organic Synthesis,[4] a large number of reviews on related topics have been published. Thus, a number of overviews on wider spectra of organic reactions (carbon–carbon bond formation,[5] cycloaddition reactions,[6,7] and three-membered ring formation processes)[8] have appeared. Applications of metal–carbene complexes in organic synthesis in general[3,9–11] or using asymmetric approaches[12–14] have been systematized. Several reviews dedicated to transition metal-catalyzed cyclopropanation reactions by using general[15–21] or asymmetric[22–29] approaches have also been published. Some reviews on the methodology of cyclopropanation reactions[30] and their application in organic synthesis[31,32] have appeared. The use of ketocarbenoids for the synthesis of substituted (such as nitro-,[33] trifluoromethyl-,[34] and donor–acceptor)[35,36] cyclopropanes has also been analyzed in several reviews.

This chapter will focus on the addition of ketocarbenes and ketocarbenoids to alkenes (leading to carbonylcyclopropanes), alkynes (generating carbonylcyclopropenes), and aromatic systems (initially yielding carbonylcyclopropanes, though subsequent spontaneous reactions are common). Other synthetic equivalents of ketocarbenes (such as α-halocarbonyl compounds in base-catalyzed reactions with electron-poor olefins or 2-oxoalkyl carbonates in Pd(0)-catalyzed reactions with norbornenes) have not been considered here.

4.20.2 Reaction Mechanisms

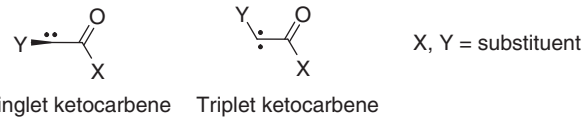
4.20.2.1 Properties of Ketocarbenes

Ketocarbenes can be generated by photolysis or thermolysis of carbonyl-bearing derivatives of diazo compounds,[37,38] diazirines,[39] cyclopropanes,[40,41] cyclopropenes,[42] or ylides[43] (Scheme 1). However, low stereoselectivities and serious interference of competing reactions are usually observed in cyclopropanation reactions involving ketocarbenes.



Scheme 1

Both singlet and triplet spin states are possible for ketocarbenes. Singlet carbenes are usually obtained through thermal or photochemical decomposition of the corresponding diazo compounds. An orthogonal carbonyl/carbene arrangement is found in singlet ketocarbenes, such as formylcarbene (**1**) (X=Y=H),[44] chloro(methoxycarbonyl)carbene (**2**) (X=OMe, Y=Cl),[40] and phenyl(methoxycarbonyl)carbene (**3**) (X=OMe, Y=Ph).[45] Singlet ketocarbenes show a typical electrophilic behavior, undergoing a number of reactions (such as ylide formation with tertiary amines or O–H insertion with alcohols)[46] with a limited synthetic interest because of the competition with the Wolff rearrangement (activation barrier of 21 kJ mol^{-1}, according to theoretical calculations on formylcarbene (**1**)).[44]



Triplet ketocarbenes are usually obtained from the singlet analogs through intersystem crossing.[47] Interestingly, a coplanar arrangement has been theoretically predicted for a number of triplet carbonyl carbenes (X=H, OH, OMe; Y=H, F, Cl).[48] However, the synthetic interest of triplet ketocarbenes is usually scant because of their high reactivity as diradicals. Thus, whereas cyclopropanation reactions of singlet ketocarbenes are stereospecific relative to the alkene substituents, the analogous processes of triplet carbonyl carbenes are not.[43,49]

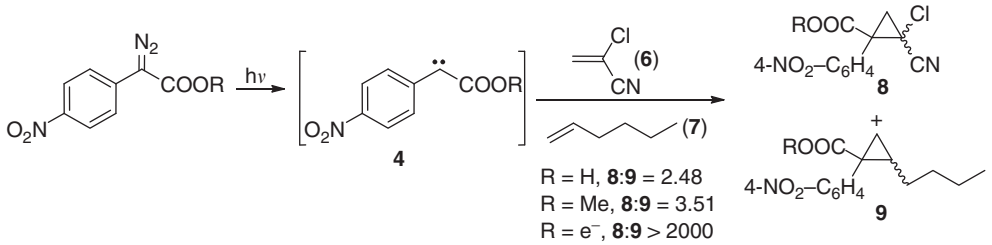
Singlet carbonyl carbenes can be stabilized by π-donor substituents. Thus, whereas the singlet state of 4-nitrophenyl(methoxycarbonyl)carbene (X=OMe, Y=4-NO_2–C_6H_4–, **4**) is theoretically disfavored by 25.5 kJ mol^{-1} in comparison with the triplet analog, singlet state of 4-aminophenyl(methoxycarbonyl)carbene (X=OMe, Y=4-NH_2–C_6H_4–, **5**) is preferred by 11.7 kJ mol^{-1}.[45]

The alkene affinity of ketocarbenes is affected by the electronic properties of the substituents on the carbonylic moiety, as shown in a competitive kinetic study on the reactions of carbenes derived from 4-nitrophenyldiazoacetic acid derivatives toward an electron-deficient alkene (α-chloroacrylonitrile, **6**) and an electron-rich olefin (1-hexene, **7**). Thus, whereas moderate preferences for **6** have been found for the corresponding acid and methyl ester, a huge selectivity has been observed for the corresponding carboxylate anion (Scheme 2).[50]

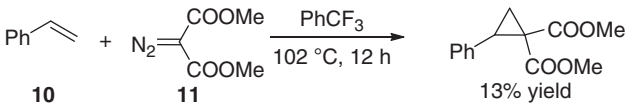
4.20.2.2 Thermal Reactions Through Ketocarbenes

4.20.2.2.1 Diazo compounds

The synthetic utility of noncatalyzed cyclopropanation reactions is strongly dependent on the thermal stability of these reagents. Thus, a poor yield (13%) was obtained for the styrene **10**+dimethyl diazomalonate **11** reaction because of the low decomposition rate of the diazo compound (equation 1).[51]

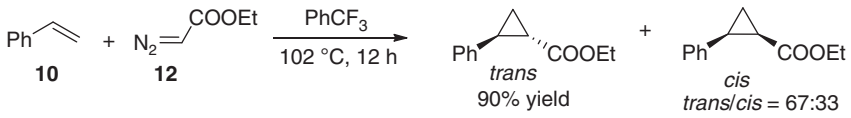


Scheme 2



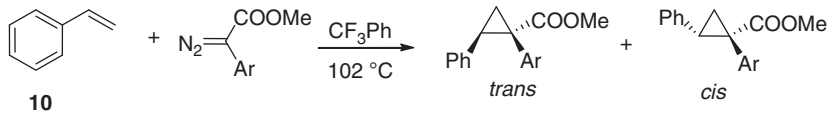
(1)

Instead, a good result (90%) was obtained in the analogous reaction using ethyl diazoacetate **12** (equation 2).[51]



(2)

Aryldiazoacetic esters Ar–CN_2–COOMe have been successfully used in thermal cyclopropanation reactions with styrene **10** (93% yield for Ar=4-methylphenyl) (equation 3).[51] Interestingly, *trans*/*cis*-selectivities of such reactions are strongly dependent on the electronic properties of the aryl substituents. Thus, high diastereoselectivities are found in cyclopropanation reactions involving aryldiazoacetic esters bearing electron-donor groups (*trans*/*cis*=95:5 for Ar=4-methylphenyl, 4-methoxyphenyl, and 3,4-dimethoxyphenyl), whereas poor results are found for those substituted by electron-withdrawing groups (*trans*/*cis*=56:44 for Ar=4-nitrophenyl).



(3)

However, the nature of the alkene seems to be less critical, and thus high diastereoselectivities have also been observed in thermal cyclopropanation reactions of a number of substrates using some aryldiazoacetic esters bearing electron-donor substituents (Table 1).[51]

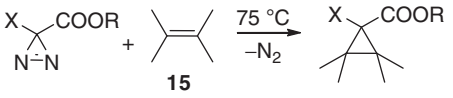
Table 1 Results of the thermal reactions between different substrates and some methyl aryldiazoacetates $ArCN_2COOMe$[51]

Substrate	*Ar*	*Yield (%)*	trans/cis
p-Methylstyrene	4-MeO-C_6H_4	58	92:8
p-Chlorostyrene **163**	4-MeO-C_6H_4	88	95:5
Butyl vinyl ether **13**	4-MeO-C_6H_4	85	86:14
2,3-Dihydrofuran	3,4-$(MeO)_2$-C_6H_3	71	>95:5
cis-β-Methylstyrene	3,4-$(MeO)_2$-C_6H_3	72	92:8
trans-β-Methylstyrene	3,4-$(MeO)_2$-C_6H_3	62	>95:5
1,2-Dihydronaphthalene	3,4-$(MeO)_2$-C_6H_3	50	>95:5
Phenylacetylene **14**	3,4-$(MeO)_2$-C_6H_3	44	–

Reactions carried out in $PhCF_3$ at 102 °C.

4.20.2.2.2 Diazirines

Diazirines are potentially shock sensitive and should be handled with extreme caution. Nevertheless, high cyclopropane yields have been obtained in the thermal decomposition of some (alkoxycarbonyl)halodiazirines in tetramethylethylene **15** (equation 4).[39]

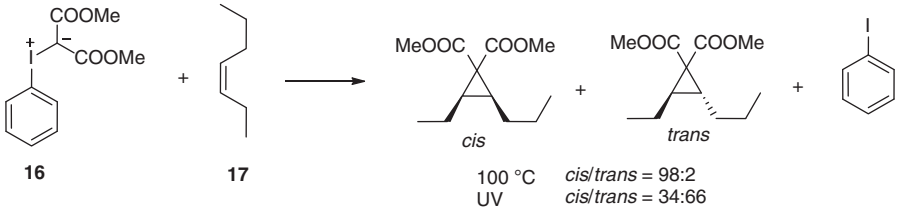


X	R	yield (%)
Cl	Me	89
Cl	Bu	94
Br	Me	89
Br	Bu	96

(4)

4.20.2.2.3 Ylides

Cyclopropanation reactions can be carried out by thermal or photochemical dissociation of ketocarbenoid ylides. The reaction stereoselectivity relative to the alkene substituents is dependent on the spin multiplicity of the ketocarbene intermediate. Thus, the cyclopropanation reaction of bis(methoxycarbonyl)carbene-iodobenzene ylide **16** with *cis*-3-heptene **17** was achieved with a high stereochemistry conservation rate (98%) by heating at 100 °C (in agreement with the predominance of a singlet ketocarbene). In contrast, a low conservation rate (34%) was obtained under photolytic conditions, consistently with the preference for a triplet ketocarbene (equation 5).[43]

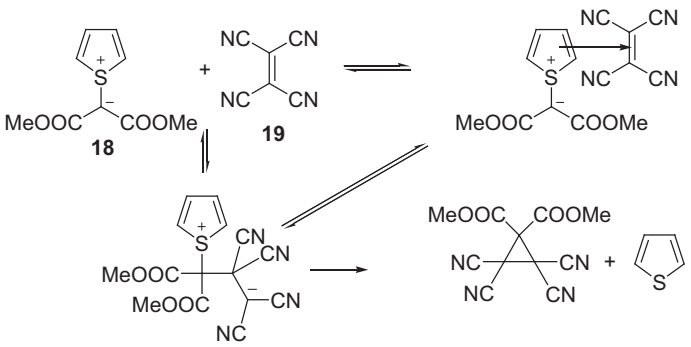


(5)

4.20.2.3 Thermal Reactions Through Zwitterions

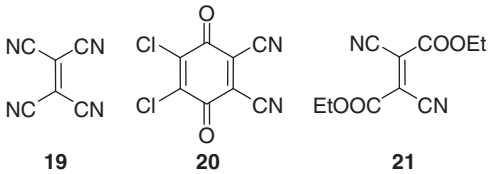
Zwitterions can be used as starting materials in cyclopropanation reactions or can be generated *in situ* in the reaction mixtures (typically under basic conditions from an onium salt). In contrast with the electrophilic nature of most ketocarbenes and metal-bound ketocarbenoids, a nucleophilic behavior is typically observed in ketocarbenoid ylides, as a consequence of the occurrence of a carbonyl-conjugated anionic carbon atom bound to an onium heteroatom. As a consequence, electron-poor alkenes can be efficiently cyclopropanated using ketocarbenoid ylides without the need of a catalyst.

A stepwise reaction mechanism involving a zwitterionic intermediate is the most common pathway in cyclopropanation reactions of ylides with electron-deficient alkenes. Interestingly, the reversible formation of an ylide–olefin charge-transfer complex has been observed as a competitive reaction in the thiophenium bis(methoxycarbonyl)methylide **18** versus tetracyanoethylene **19** reaction (Scheme 3).[52]

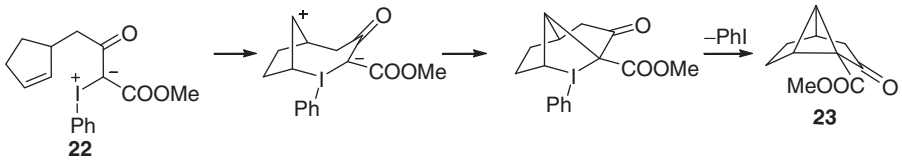


Scheme 3

The alkene reactivity of thermal cyclopropanation reactions with ylides is dependent on the number and electron-withdrawing ability of the olefin substituents. Thus, the reactivity of several alkenes with thiophenium bis(methoxycarbonyl)methylide (**18**) showed the following reactivity order: tetracyanoethylene (**19**) > 2,3-dichloro-5,6-dicyanobenzoquinone (**20**) > diethyl dicyanofumarate (**21**).[52]



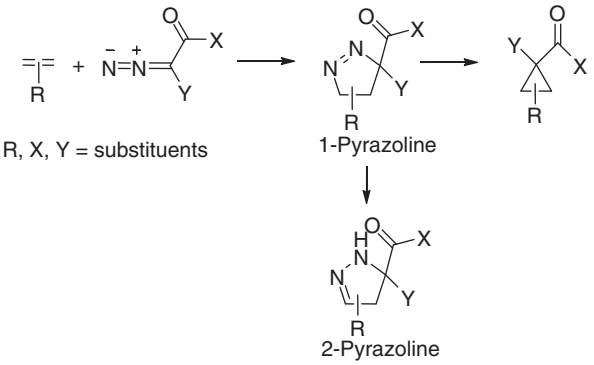
A mechanism involving reductive elimination of a heterocycle may be involved in some cyclopropanation reactions of ylides. As an example, the intramolecular electrophilic attack of the positive iodine to the C=C bond of **22** followed by (or simultaneous to) attack by the enolate on the carbocationic carbon in a noncatalyzed intramolecular reaction generates ioda(III)cyclobutane, which undergoes a reductive elimination to generate the resulting cyclopropane **23** (Scheme 4).[53,54]



Scheme 4

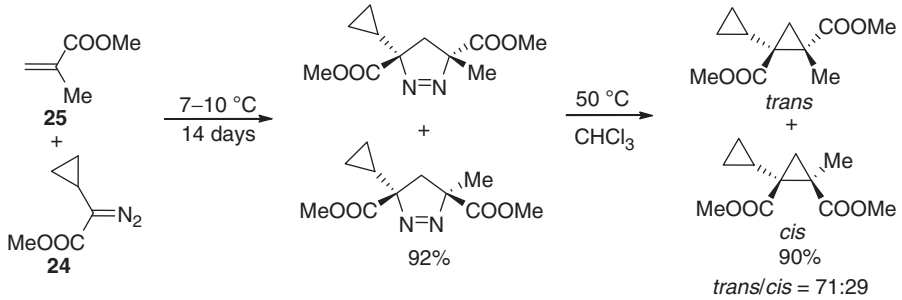
4.20.2.4 Thermal Reactions Through Pyrazolines

A mechanism involving some pyrazoline intermediates may also participate in some cyclopropanation reactions of diazo compounds. Thus, α-diazocarbonyl compounds can react with electron-deficient alkenes through thermal 1,3-dipolar cycloaddition reactions to yield initially 1-pyrazolines,[55] though such heterocycles can extrude dinitrogen to generate cyclopropanes in a spontaneous way[56] or by subsequent heating.[57,58] Nevertheless, the usefulness of the pyrazoline path for a general method of obtaining cyclopropanes is limited by the possible competitive tautomerization of the originally formed 1-pyrazoline to a 2-pyrazoline, which cannot extrude dinitrogen (Scheme 5).



Scheme 5

Thermal cyclopropanation reactions through pyrazolines can be very useful in organic synthesis as the typical substrates (electron-poor olefins) are usually unreactive under conventional transition-metal catalysis. Thus, the reaction between methyl cyclopropyldiazoacetate **24** and methyl methacrylate **25** led to a diastereomixture of pyrazolines that generated the corresponding cyclopropanes by mild heating (Scheme 6).[58] The high cyclopropane yield observed in this reaction can be attributed to the impossibility of tautomerization of the intermediate pyrazolines. In contrast, products from cyclopropane ring opening were exclusively obtained using Rh or Cu catalysts.

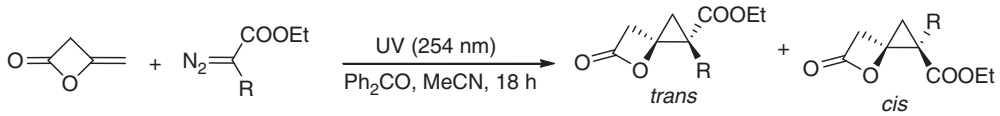


Scheme 6

4.20.2.5 Photochemical Reactions

High reactivities and low selectivities are usually observed in reactions involving photochemically generated ketocarbenes. Thus, an almost indiscriminate reactivity of laser flash generated (ethoxycarbonyl)carbene toward alkenes (cyclopropanation), alcohols (O–H insertion), ethers, or sulfides (ylide formation) was observed.[59] Similarly, a very low discrimination was also found in cyclopropanation reactions of singlet bis(methoxycarbonyl)carbene with a variety of alkenes.[60]

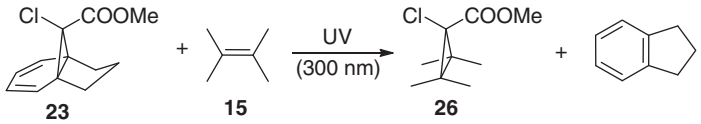
Photochemical cyclopropanation reactions have been scarcely used for synthetic purposes in the last years. As an example, two diazoesters were separately irradiated at 254 nm in the presence of diketene and benzophenone to generate the corresponding mixtures of spirolactones with modest yields and selectivities (equation 6).[61]



R	yield (%)	*trans*/*cis*
Me	30	57:43
Pr^i	44	59:41

(6)

Ultraviolet (UV) irradiation of certain cyclopropanes has been used for generating ketocarbenes. Thus, chloro(methoxycarbonyl)carbene **2**, obtained from irradiation at 300 nm of an indane cyclopropane derivative **23**, has been trapped by tetramethylethylene **15** to yield a new cyclopropane **26** (equation 7).[40]

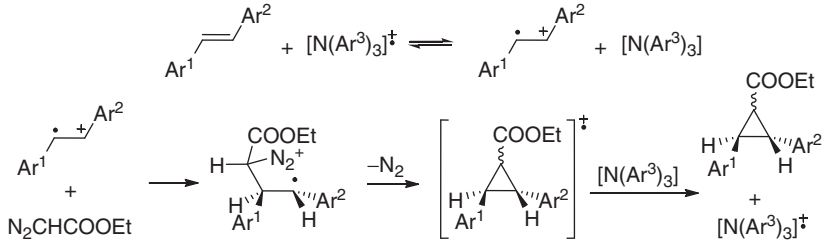


23 **15** **26**
85% yield

(7)

4.20.2.6 Cationic Radical-Catalyzed Reactions

The mechanism of triaryl aminium hexachloroantimonate-catalyzed cyclopropanation reactions of a set of substituted stilbenes with ethyl diazoacetate **12** was studied in detail by Yueh and Bauld.[62] A catalytic cycle involving a cationic radical mechanism was proposed for such reactions, consistent with a number of experimental data (**Scheme 7**). Thus, the formation of a stilbene cationic radical as the determining rate step in a reversible equilibrium involving the catalyst is supported by isotopic deuterium effects data. Binding to the diazo compound generates a carbocation radical intermediate which subsequently losses N_2 to yield a cyclopropane cationic radical. The cyclopropane electron hole can be transferred to a new stilbene molecule in a chain mechanism. The catalyst is finally regenerated by electron transfer between a cationic radical and triarylamine.



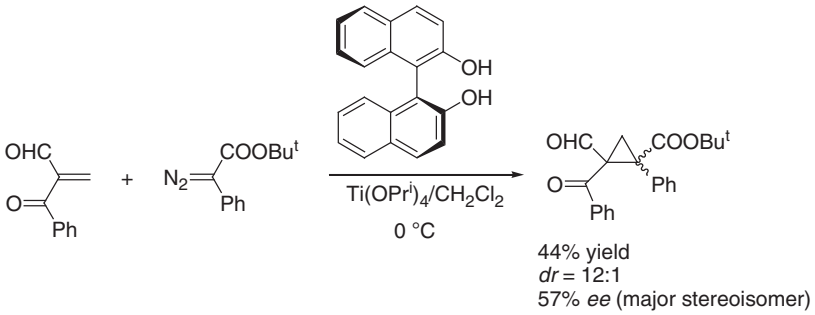
Scheme 7

The synthetic interest of cationic radical-catalyzed reactions is essentially limited to a number of reactive alkenes (substituted styrenes[63] and stilbenes,[62] conjugated dienes,[64] and tetrasubstituted alkenes)[65] as substrates. Thus, typical alkenes (such as norbornene **27** or 1-octene **28**) are not reactive enough to be cyclopropanated by using this method.[64]

4.20.2.7 Lewis Acid-Catalyzed Reaction

A number of cyclopropanation reactions of electron-deficient olefins with α-diazo carbonyl compounds can be catalyzed by Lewis acids. Thus, some reactions between *tert*-butyl aryldiazoacetates and α-substituted acroleins have been catalyzed by BF_3, $TiCl_4$, or

$SnCl_4$.[66] The Lewis acid–enal complex is assumed to be a key reaction intermediate, which can undergo the diazoester attack and N_2 loss through a stepwise or concerted mechanism. Moderate to high enantioselectivities have been obtained in cyclopropanation reactions catalyzed by chiral Lewis acids, such as Ti binolate[66] (equation 8), or a chiral oxazaborolidinium salt **29** (equation 9).[67]



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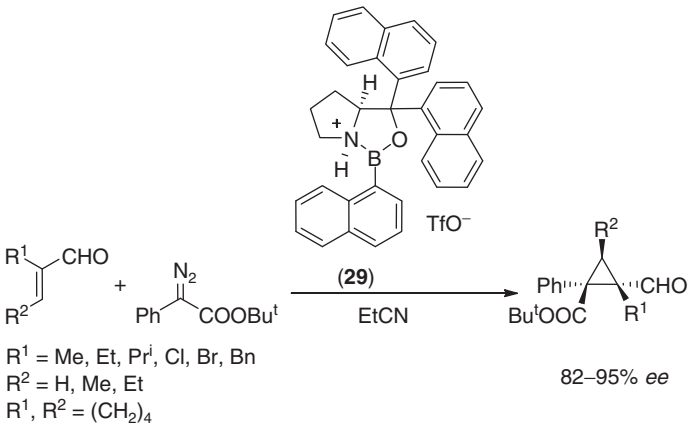
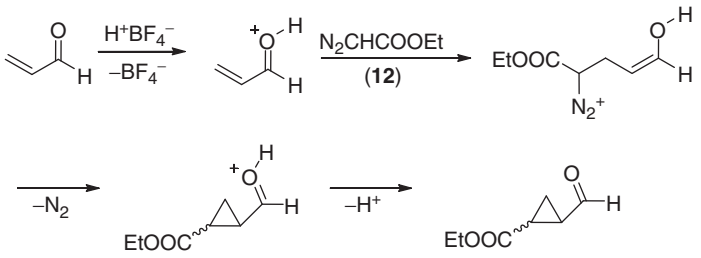


(9)

4.20.2.8 Brønsted Acid-Catalyzed Reaction

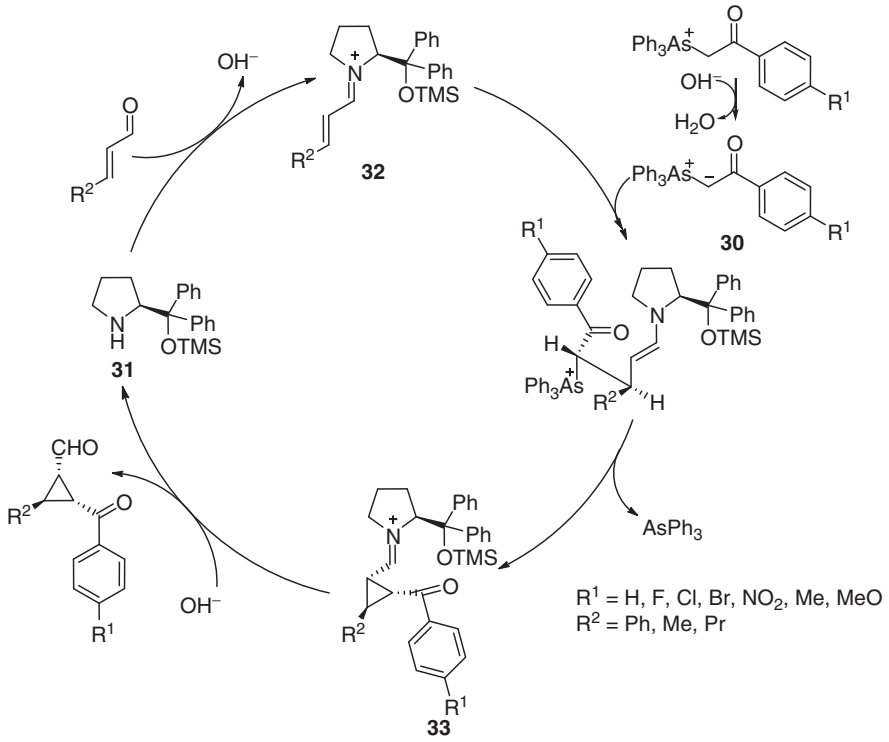
The cyclopropanation reactions of some 2-enals with ethyl diazoacetate **12** catalyzed by strong Brønsted acids (such as HBF_4[68] or TfOH)[66] have been studied. In the HBF_4-catalyzed reaction involving acrolein, protonated aldehyde is assumed as a reaction intermediate which can be attacked by ethyl diazoacetate **12** to yield a diazonium reaction intermediate, which generates a protonated formylcyclopropane derivative by dinitrogen extrusion (Scheme 8).



Scheme 8

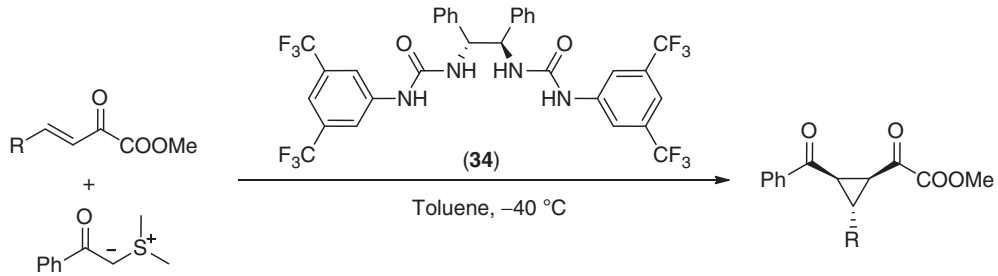
4.20.2.9 Organocatalysis

Electron-poor olefins can be cyclopropanated in nonasymmetric and asymmetric ways using ylides by means of organocatalysis.[69,70] As an example, the organocatalytic cyclopropanation reaction of *α,β*-unsaturated aldehydes with an *in situ*-generated arsorane **30** has been interpreted as a consequence of the reaction of the aldehyde with cyclic amine **31** leading to the formation of an allylidene-ammonium ion **32** that can be attacked by ylide **30**, affording an iminium cyclopropane **33** through triphenylarsine loss, the iminium ion being subsequently hydrolyzed and the catalyst being regenerated (Scheme 9).[71]



Scheme 9

Good results have been obtained in the cyclopropanation reactions between some substituted β,γ-unsaturated α-ketoesters and a phenacyl sulfonium ylide using chiral urea **34** as a catalyst (Scheme 10; Table 2).[72]

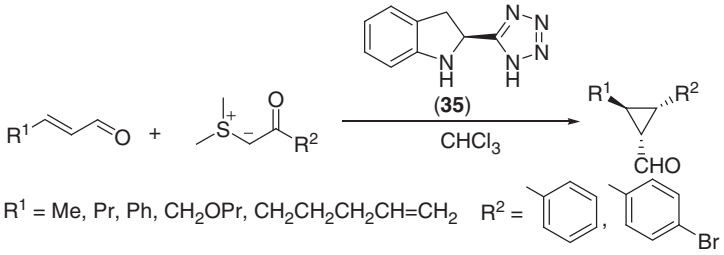


Scheme 10

Table 2 Results of cyclopropanation reactions of some substituted β,γ-unsaturated α-ketoesters and phenacyl dimethylsulfonium ylide by using **34** as a catalyst (Scheme 10)[72]

R	*Yield (%)*	dr	ee *(%)*
Ph	81	89:11	70
4-$MeOC_6H_4$	54	94:6	60
4-MeC_6H_4	61	90:10	66
4-FC_6H_4	55	88:22	66
4-ClC_6H_4	57	88:22	62
4-BrC_6H_4	52	88:22	60
3-BrC_6H_4	49	91:9	54
2-FC_6H_4	56	83:17	62
2-ClC_6H_4	58	90:10	70
PhCH=CH	35	67:33	80

Excellent stereoselectivities ($dr > 98{:}2$ and % $ee = 99\%$), with good yields (≥74%) have been obtained in several cyclopropanation reactions of 2-enals by using sulfonium ylides as ketocarbenoids and (*S*)-2-(1*H*-tetrazol-5-yl)indoline **35** as an organocatalyst (equation 10).[73]

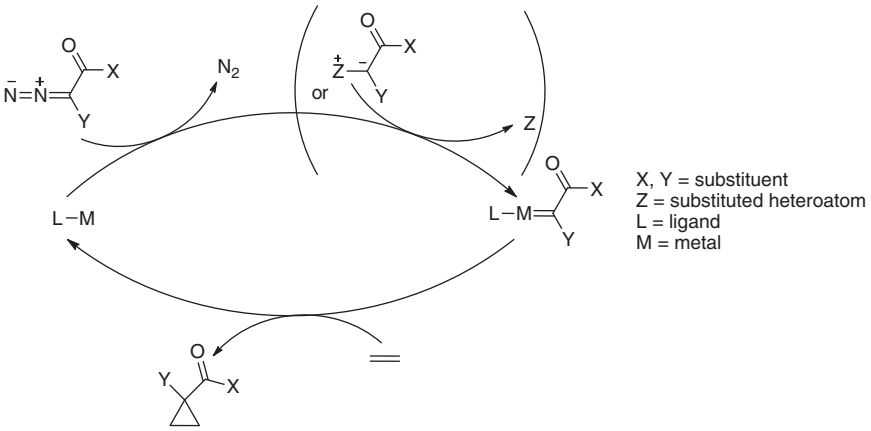


(10)

4.20.2.10 Reactions Involving Transition Metal–Carbene Complexes

Because of the electrophilic nature of typical metal–ketocarbene complexes, a preference for electron-rich alkenes is usually observed in catalyzed cyclopropanation reactions.[6] Instead, very low yields are typically obtained in transition metal-catalyzed cyclopropanation reactions of electron-deficient olefins.

The mechanism of cyclopropanation reactions involving transition metal–carbene complexes can be interpreted in terms of a catalytic cycle involving two major phases: the reaction of catalyst with the carbene precursors (diazo compound or ylide) to afford a metal–carbene complex and the subsequent reaction of the later with an alkene to yield the corresponding cyclopropane, thus regenerating the catalyst (Scheme 11).



Scheme 11

4.20.2.10.1 Formation of the metal–carbene complex

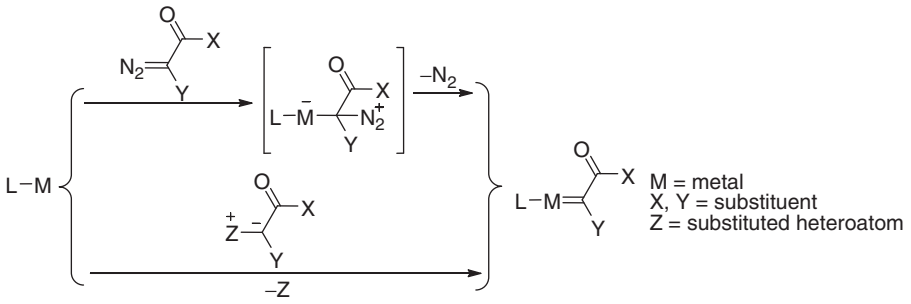
Although most metals are added to reaction mixtures in those oxidation states which are active in the catalytic cycle, some metal complexes are reduced in the reaction medium before becoming catalytically active species. Thus, the reduction of Cu(II) to Cu(I) takes place either through spontaneous oxidation of the diazo compound (used as a reactant) or through addition of reductants, such as phenylhydrazine[74] or diisobutylaluminum hydride.[75] Similarly, the reduction of Pd(II) to Pd(0) can be achieved by reaction with either the catalytic mixture $Pd(acac)_2/PPh_3/AlEt_3$[76] or the diazo compound itself.[77]

In reactions catalyzed by some metal complexes (such as Cu[78] or Rh[79] derivatives), a preequilibrium involving the alkene coordination to the metal can be established (Scheme 12). As a consequence, a decrease on the cyclopropanation reaction rate is found when a raised olefin concentration is applied.[80]

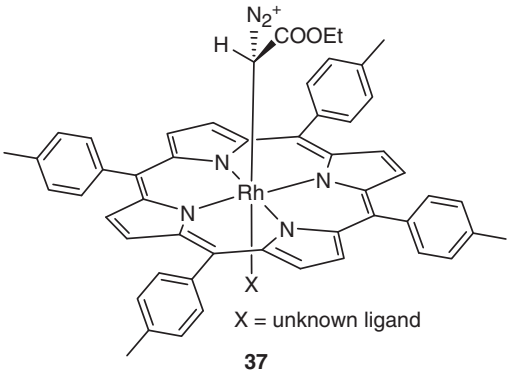
The metal catalyst reacts with a carbene precursor (such as a diazo compound or an ylide) to generate the corresponding metal–carbene complex, as shown by a kinetic study on $Rh_2(OAc)_4$ **36**-catalyzed cyclopropanation reactions of diazo compounds and iodonium ylides (Scheme 13).[81]

A diazo compound–metal complex bearing a metal–carbon bond is subsequently formed (as found in the Rh–porphirin–ethyl diazoacetate complex **37**).[79] Dinitrogen extrusion of such a complex leads to a metal–carbene reaction intermediate (as characterized by nuclear magnetic resonance (NMR) for the copper–methyl phenyldiazoacetate complex **38**).[82]

Scheme 12



Scheme 13



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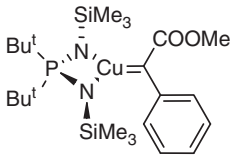
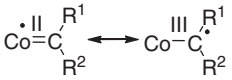


38

A number of metal–ketocarbene complexes have been isolated and characterized by X-ray diffraction,[83,84] showing an orthogonal M=C–C=O arrangement, which indicates a lack of conjugation between two double bonds.

Most typical metal–ketocarbene complexes (such as Cu(I) derivatives)[85] participating in the cyclopropanation reactions are diamagnetic, acting as synthetic equivalents of singlet carbenes. However, carbene complexes of Co(II)[86] metals are paramagnetic, showing a radicaloid character on the carbene carbon atom, analogous to the triplet carbenes.



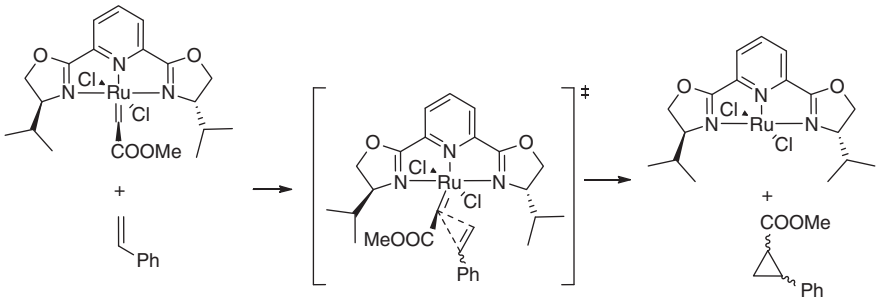
4.20.2.10.2 Reaction of the metal–carbene complex

Three alternative mechanisms (direct insertion, stepwise insertion, and metallacycle pathway) can be considered for the cyclopropanation reaction of metal–carbene complex with an alkene.

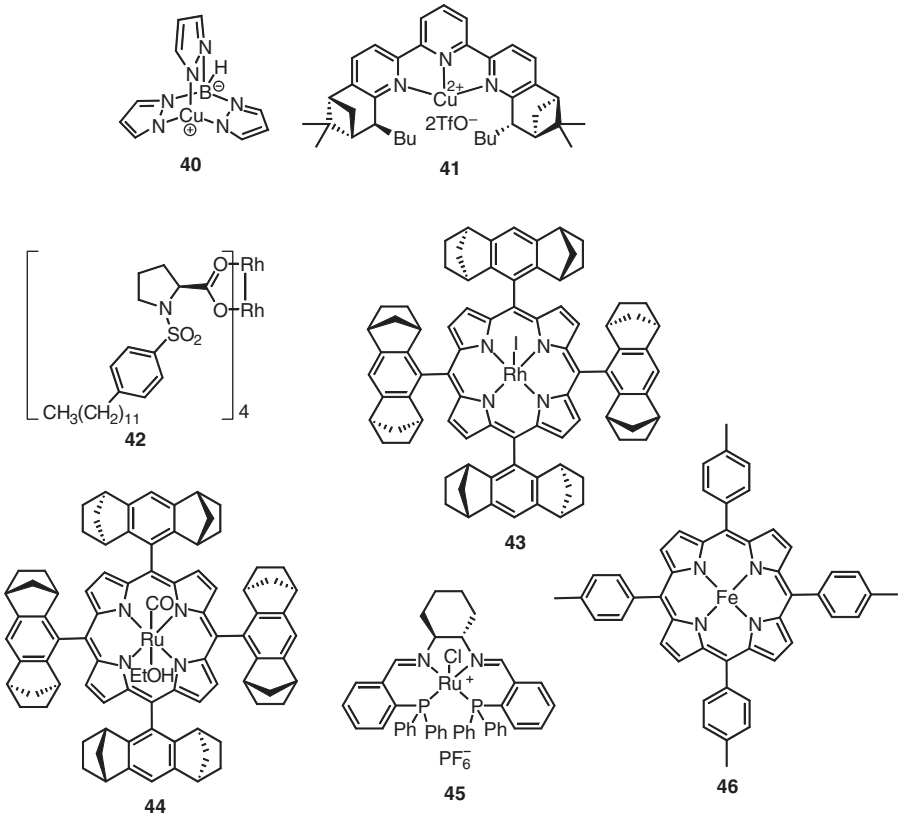
4.20.2.10.2.1 Direct insertion

In many cases, the metal–carbene complex reacts with the alkene through the simultaneous formation of both the new C–C bonds (e.g., see Scheme 14).[84,87] As such a step is typically very exothermic, and very early transition states are common.[84,88] Typical transition states show an approximately planar M=C versus olefin arrangement as well as an asynchronous approximation, according to theoretical calculations.

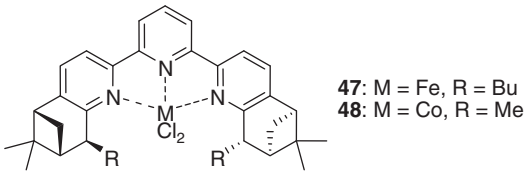
An electrophilic behavior of metal–carbene complexes has been inferred from Hammett studies on cyclopropanation reactions between a diazo compound (as ethyl diazoacetate **12** or methyl phenyldiazoacetate **39**) and some sets of substituted styrenes by using a number of catalysts derived from Cu (**40**,[89]**41**),[90] Rh (**42**,[91]**43**),[92] Ru (**44**,[93]**45**),[94] and Fe (**46**).[95]



Scheme 14



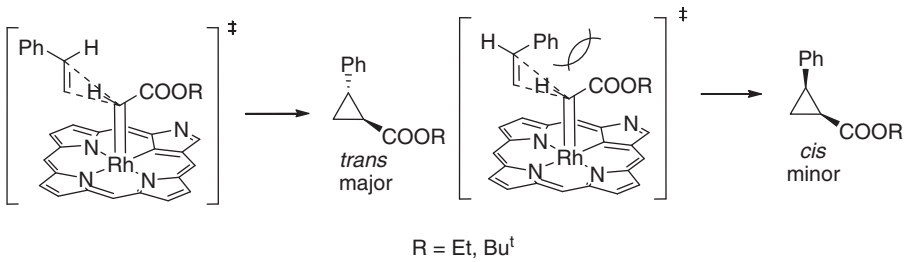
Instead, the nucleophilic behavior for metal–carbene complexes observed in the reactions of ethyl diazoacetate **12** with some substituted styrenes and using some Fe (**47**) or Co (**48**) catalysts[96] can be attributed to a radical-like behavior of the complex.



47: M = Fe, R = Bu
48: M = Co, R = Me

The *trans* preference observed in many cyclopropanation reactions is usually attributed to the occurrence of steric hindering between the oxo functional group and the olefin alkyl substituent in the *cis*-transition state (**Scheme 15**).[97]

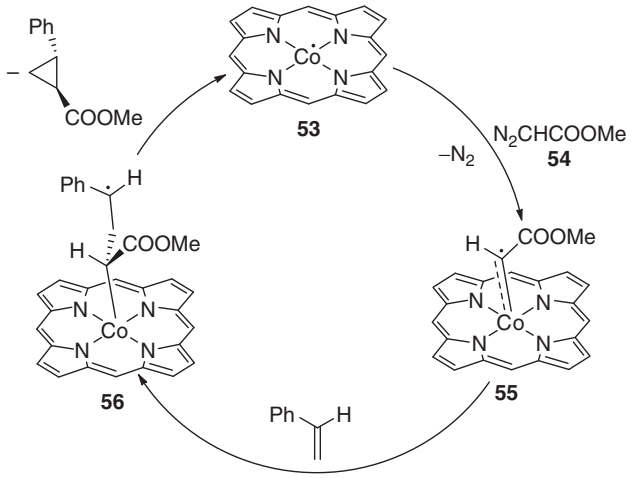
A comparison between the relative rates of several $Rh_2(OAc)_4$ **36**-catalyzed cyclopropanation reactions of ethyl diazoacetate **12** for substituted olefins shows the reactivity order butyl vinyl ether **13** (8.6) > styrene **10** (3.5) > cyclohexene **49** (2.5) > 2,5-dimethylhexa-2,4-diene **50** (2.1) > 2-methylbut-2-ene **51** (1.5), vinylacetate **52** (1.1), 1-hexene **52** (1.0).[91] Hence, an activating effect alkoxy > aryl > acyloxy≈alkyl can be inferred for the alkene substituents in cyclopropanation reactions through direct insertion.



Scheme 15

4.20.2.10.2.2 Stepwise insertion

Some cobalt–carbene complexes can undergo a stepwise diradicaloid reaction with olefins, according to theoretical (Scheme 16)[86] and experimental studies.[98] Thus, the porphyrin–cobalt complex **53** reacts with methyl diazoacetate **54** to yield the corresponding carbene complex **55**, subsequently reacting with styrene **10** to yield the radical reaction intermediate **56,** which regenerates the original catalyst **53** by loss of the corresponding cyclopropane (Scheme 16). As an interesting consequence of the diradicaloid reaction mechanism, electron-poor olefins can be efficiently cyclopropanated using Co(II) catalysts.



Scheme 16

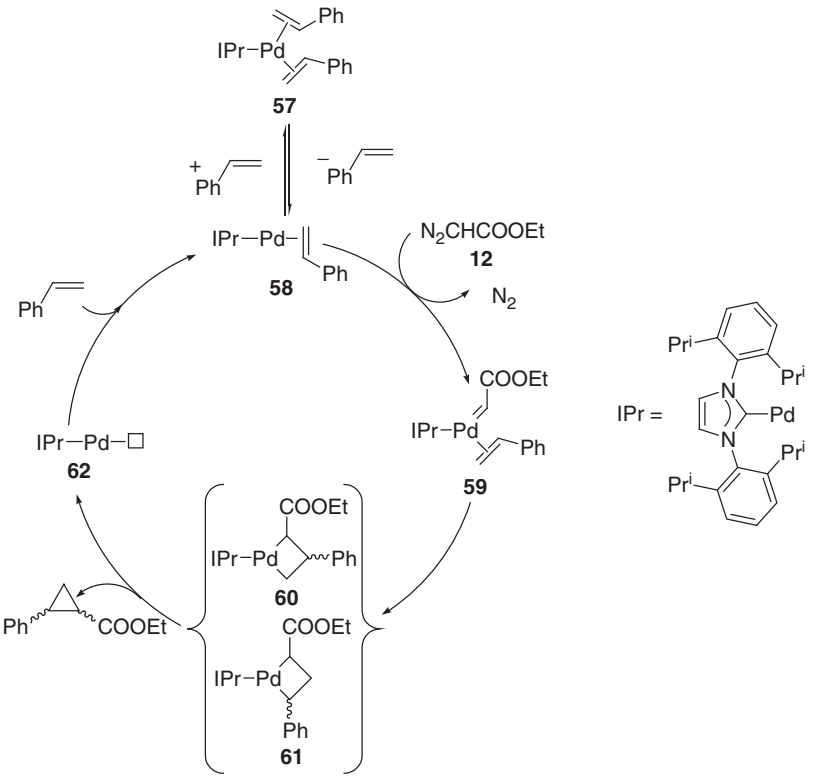
4.20.2.10.2.3 Metallacycle pathway

A metallacycle mechanism can take place in some metal-catalyzed cyclopropanation reactions. According to this pathway, the reaction between the metal–carbene species and olefin takes place through a formal [2+2] cycloaddition leading to a metallacyclobutane, which subsequently undergoes a reductive elimination to yield the resulting cyclopropane.

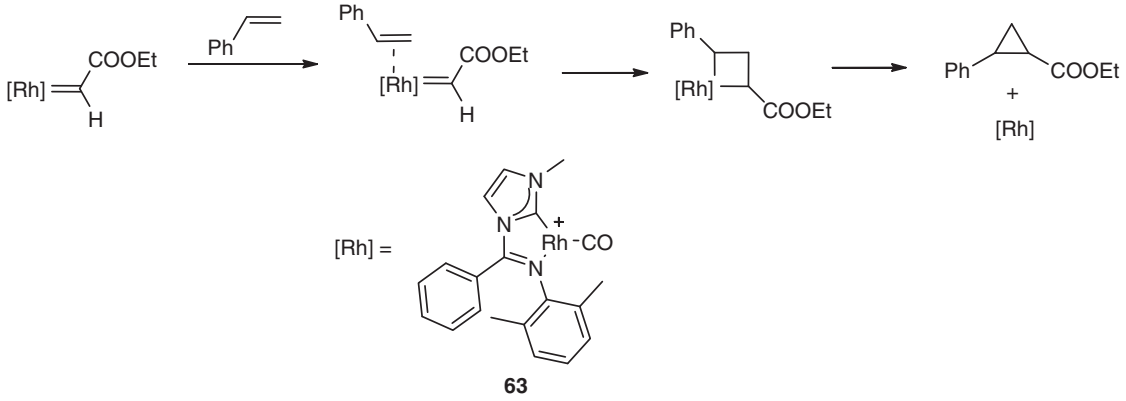
As a representative example of this mechanism, a Pd(0)-catalyzed reaction between styrene **10** and ethyl diazoacetate **12** can be considered (Scheme 17).[99] Thus, the catalyst precursor IPrPd(styrene)$_2$ **57** can loss a styrene molecule through a reversible equilibrium to yield IPrPd(styrene) **58**, which can react with ethyl diazoacetate **12** to generate a styrene-coordinated Pd ketocarbenoid, whereas N_2 is evolved. The styrene-coordinated Pd ketocarbenoid **59** can undergo an intramolecular [2+2] cycloaddition to yield one or two regioisomeric palladacyclobutanes (**60**, **61**). Reductive elimination of these metallacycles generates the resulting cyclopropanes as well as a Pd complex having a coordinative vacant (**62**), which can subsequently react with a new styrene molecule to regenerate IPrPd(styrene) **58**.

Some metals other than palladium can be involved in cyclopropanation reactions via metallacycles. Thus, a detailed theoretical study on a cyclopropanation reaction between styrene **10** and ethyl diazoacetate **12** catalyzed by a cationic Rh complex bearing a *C,N*-ligand (**63**) has shown the feasibility of the metallacycle pathway (Scheme 18), whereas the direct insertion mechanism could not operate.[100]

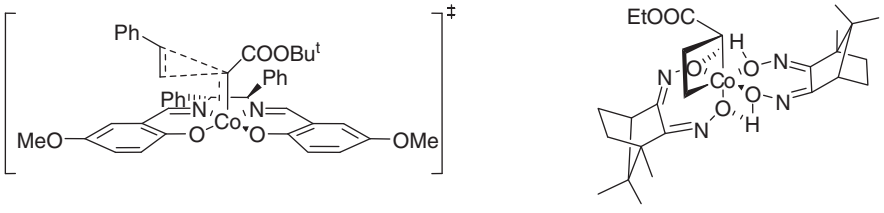
Preference for alternative mechanisms in cyclopropanation reactions involving metal–carbene complexes can be altered by geometrical constraints. Thus, according to theoretical calculations Co-catalyzed cyclopropanation reactions have shown that the concerted mechanism is favored for complexes showing a nearly coplanar environment, whereas the metallacycle pathway being preferred otherwise (see Scheme 19).[101] Nevertheless, the most common scene is illustrated by a theoretical study of an intermolecular Cu(I)-catalyzed reaction: both mechanisms being possible, direct insertion is slightly favored.[84]



Scheme 17



Scheme 18



Scheme 19

4.20.3 Ketocarbenoid Precursors

Diazo compounds and α-amino-α,β-unsaturated carbonyl compounds have been included in this section as ketocarbenoid precursors. Ylides have also been discussed here as precursors of metal–carbene complexes for a general overview despite many cyclopropanation reactions involving ylides are carried out in the absence of transition-metal derivatives.

4.20.3.1 Diazo Compounds

A number of reviews dealing on the synthetic applications of diazo compounds as a whole[102–104] or specifically dedicated to α-diazocarbonyl derivatives,[55,105–111] and dicarbonyl diazo compounds[112] have been recently published. As a general rule, extreme caution should be exercised when handling α-carbonyl diazo compounds as violent detonation properties have been reported for a number of such reactants (diazoacetaldehyde **64**,[113] ethyl diazoacetate **12**,[114] diethyl diazomalonate **65**).[115] Here, the different families of diazo compounds that have been used as ketocarbenoid precursors in carbenoid addition reactions only are reviewed. Further information about the reactions of diazo compounds will be found in Sections 4.20.5 and 4.20.6.

4.20.3.1.1 Monocarbonyl-substituted diazo compounds

4.20.3.1.1.1 Diazoaldehydes

Although the reactivity of diazoacetaldehyde **64** has been reviewed,[113] no experimental cyclopropanation reactions involving diazoaldehydes have been recently reported.

4.20.3.1.1.2 Diazoketones and bis(diazo)ketones

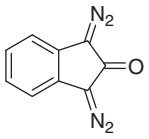
The reactivities of diazoacetone **66**[113] and diazoacetophenone **67**[113] (including cyclopropanation reactions) have been reviewed. A number of 1-diazoalkan-2-ones N_2CHCOR have been reacted with different olefins in the presence of transition-metal catalysts, though moderate yields have been generally obtained because of the occurrence of a number of competing reactions (see Section 4.20.4.1.1).

Ethyl diazopyruvate **68** reacted with a number of electron-rich alkenes in the presence of $Rh_2(OAc)_4$ **36** to yield the corresponding cyclopropanes in moderate yields.

Special interest has been paid on cyclopropanation reactions of diazoacetophenone **67**[113] because of the lack of C_{sp^3}–H bonds (hence, avoiding competing C–H carbene insertion reactions, see Section 4.20.4.1.1.3). Diazoacetophenone **67** has been used in catalyzed cyclopropanation reactions of some substituted derivatives of diketene[61,116] and styrene,[117–119] though low yields are obtained in many cases because of the competition of carbene dimerization (see Section 4.20.4.1.1.1).[117,118]

Other diazoketones used as carbenoid precursors are 1-aryl-1-diazoalkan-2-ones,[120] 1-aryl-1-diazoalk-3-yn-2-ones,[121] hetaryldiazoketones,[122] diazocycloalkanones,[123] 2-diazo-1-indanone,[124] and substituted diazooxotetrahydroindazoles.[125]

UV irradiation of 1,3-bis(diazo)indan-2-one **69** in neat benzene by using a mercury lamp afforded the bis-norcaradiene product in 51% yield.[126]



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4.20.3.1.1.3 Diazoesters and diazothioesters

The chemistry of diazoacetic esters as a whole[127] and some particular compounds (methyl diazoacetate **54**,[113] ethyl diazoacetate **12**)[114] have been separately reviewed. In addition to these reagents, many other $N_2CHCOOR$ compounds (R = Pr,[128] Pr^i,[129] Bu,[130] Bu^i,[131] Bu^t,[132] dicyclohexylmethyl,[133] 2,4-dimethyl-3-pentyl,[134] 2,3,4-trimethylpentan-3-yl,[135] menthyl (both enantiomers),[136] propargyl,[137] Ph,[138] Bn,[139] *trans*-2-phenylcyclohexyl,[140] (1*R*,2*S*,5*R*)-8-phenylmenthyl,[141] 2,6-dimethylphenyl,[142] 2,6-di-*tert*-butyl-4-methylphenyl,[135] cyanomethyl,[137] succinimidyl,[143] and others) have also been used in cyclopropanation reactions. Instead, the use of highly branched alkyl diazoacetates is limited by the competition of intramolecular C–H insertion reactions.[135] For extensive information about the results obtained in cyclopropanation reactions using diazoesters, see Sections 4.20.4.1.4, 4.20.4.1.5, 4.20.4.2, 4.20.5, and 4.20.6. As a brief summary, it can be said that modest to fair stereoselectivities are typically observed in catalyzed cyclopropanation reactions involving methyl **54** or ethyl **12** diazoacetates. However, a systematic raise in *trans*/*cis*-selectivity and a more irregular gain in both *trans*- and *cis*-enantioselectivities is usually obtained through the increase of the bulkiness of the diazoacetic ester alkyl group. Although some slight system-dependent variations can be found, the following hindrance order can be inferred for the most common alkyl groups of diazoacetic esters: Me≤Et < Pr^i~cyclohexyl < Bu^t≤menthyl < dicyclohexylmethyl~2,6-dimethylphenyl < 2,6-di-*tert*-butyl-4-methylphenyl.

Electronic properties of the succinimidyl group of the corresponding diazoacetic ester have been claimed to explain the increase of *trans*/*cis*-selectivity observed in an Ru-catalyzed reaction of 2-methyl-2-butene **51**.[144] However, such results can alternatively be attributed to the high steric encumbrance of succinimidyl diazoacetate **70** in a way analogous to the good stereoselectivity results observed for cyclopropanation reactions of 2,6-dimethylphenyl diazoacetate.[142] Excellent stereoselectivities have also been obtained in cyclopropanation reactions of succinimidyl diazoacetate **70** with a number of alkenes catalyzed by an Ru catalyst (see Sections 4.20.4.1.2 and 4.20.4.1.5.2.3).[145]

Ethyl diazoacetate **12** can be generated *in situ* from glycine ethyl ester hydrochloride and sodium nitrite in aqueous solution and used in cyclopropanation reactions in the presence of a number of catalysts, though lipophilic catalysts are required for obtaining high yields.[146]

High yields can also be obtained in cyclopropanation reactions using diazoesters other than diazoacetic compounds, such as α-alkyldiazoesters $RCN_2COOCHPr^i_2$[147] and aryldiazoacetates,[148–162] like methyl phenyldiazoacetate.[155,163] A Hammett study on Rh-catalyzed cyclopropanation reactions of styrene **10** with a number of substituted methyl phenyldiazoacetates has shown a larger discriminating ability toward the alkene when electron-donor substituents are present in the aryldiazoacetate.[91]

A number of hetaryldiazoacetic esters Ar–CN_2–COOMe (Ar = 4-methoxycarbonylfuran-3-yl,[164] benzofuran-3-yl,[51,165] 3-thiophenyl,[164,166] 1-Boc-indol-3-yl,[164] 2-pyridyl,[164] 6-chloro-2-pyridyl,[164] 1,4-diazinyl,[164] 3-indolyl,[167] 4,5-diphenyloxazol-2-yl,[164] benzoxazol-2-yl,[51,164] and 3-methylisoxazol-5-yl)[164] have been used in cyclopropanation reactions.

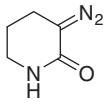
Three methyl halodiazoacetates (halogen = Cl, Br, I) have been used in cyclopropanation reactions with substituted styrenes using $Rh_2(esp)_2$ **71** in good yields (85–91%) and with high *trans*/*cis*-diastereoselectivities.[168]

Pentyl diazothioacetate was reacted with buckminsterfullerene **72** at 40 °C to yield a pyrazoline, which was subsequently pyrolized at 180 °C to afford the corresponding cyclopropane.[169] Several α-diazothioesters have been used in cyclopropanation reactions with buckminsterfullerene **72** catalyzed the mixture $Pd(acac)_2$-PPh_3-$AlEt_3$ to yield the corresponding cyclopropanes in moderate yields.[169]

4.20.3.1.1.4 Diazoamides

N,*N*-dimethyldiazoacetamide **73** has been used in cyclopropanation reactions with a number of alkynes in the presence of $Rh_2(5R\text{-MEPY})_4$ **74** to yield the corresponding cyclopropenes in fair yields and with high enantioselectivities (see Section 4.20.5.1.3).[170] A number of catalyzed cyclopropanation reactions have been carried out with the chiral Oppolzer's sultam-derived diazoacetamide **75** (see Section 4.20.4.1.5.1).[171,172]

The cyclic diazoamide 3-diazopiperidin-2-one **76** has been successfully applied in different cyclopropanation reactions.[57] On one hand, cyclopropane derivatives from electron-deficient alkenes can be formed in thermal reactions with **76** via the corresponding pyrazolines. On the other hand, cyclopropane derivatives from electron-rich olefins can be obtained through $Rh_2(OAc)_4$ **36** catalysis.



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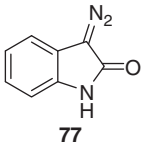
3-Diazoindolin-2-ones have revealed as versatile reactants to build substituted spirocyclopropanes. Thus, nonsubstituted 3-diazoindolin-2-one **77** has been reacted with the electron-poor olefin methyl acrylate **333** in the presence of $Pd(OAc)_2$ as a catalyst to yield the corresponding cyclopropane with a high stereoselectivity (51% yield, *cis*/*trans* > 95:5).[173] 1-Substituted derivatives of 3-diazoindolin-2-one **77** have been successfully reacted with electron-rich alkenes by using CuOTf **78** and $Rh_2(OAc)_4$ **36** as catalysts to yield the corresponding cyclopropane products.[174]



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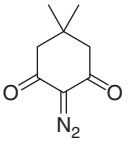
4.20.3.1.2 Dicarbonyl-substituted diazo compounds

4.20.3.1.2.1 Diazodiones

The dimedone-derived diazo compound **79** has been reacted with several alkenes (1-hexene **7**, 3,3-dimethylhex-1-ene, styrene **10**) in the presence of Rh catalysts to yield the corresponding cyclopropanes, but in modest yields (24–49%) and very low enantioselectivities (up to 16% *ee*).[175]



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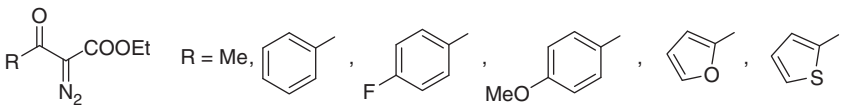
4.20.3.1.2.2 Diazoketoesters

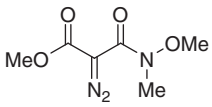
Methyl 2-diazo-3-oxobutanoate **81** reacted in the presence of some Rh catalysts with phenylacetylene **14**[176] and styrene **10**,[177] to generate the corresponding reaction products. Moreover, 3-substituted (aryl,[178] hetaryl)[179] 2-diazo-3-oxopropanoic esters have been used in Rh-catalyzed cyclopropanation reactions with different alkenes with acceptable yields (43–81%).



4.20.3.1.2.3 Diazoamideesters

Several diazoamideesters involving heterocyclic (pyrrolidine[178,180] or indole)[177,181,182] nitrogen atoms have been used in cyclopropanation reactions. A strong *trans*-directing effect by the amide group in Rh(II)-catalyzed cyclopropanation reactions of amidediazoacetic esters has been observed.[178]

The diazo derivative bearing both ester and Weinreb amide groups **82** reacted with some substituted styrenes in the presence of Rh_2(octanoate)$_4$ **83** to yield the corresponding cyclopropanes.[183]

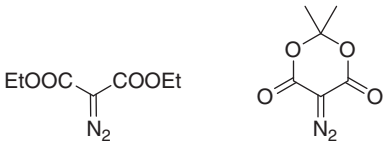


82

4.20.3.1.2.4 Diazomalonic esters

Diethyl diazomalonate **65**[115] has been used in the reactions with a number of electron-rich substrates, such as substituted styrenes,[184] allenes,[185] alkylidene lactones,[116] and phenylacetylene **14**.[176] Compound **65** has also been used in a $GaCl_3$-catalyzed cyclopropanation reaction with methyl acrylate **333** through a pyrazoline intermediate (30% yield).[186] Other diazomalonic esters (such as *tert*-butyl methyl diazomalonate, **84**)[187] have also been used in catalyzed cyclopropanation reactions.

The diazo derivative of Meldrum's acid **85** has been used successfully in some Rh_2(pivalate)$_4$ **86**-catalyzed reactions of styrene **10** and related compounds (up to 94% yield).[188]



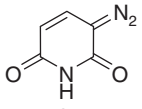
65 **85**

4.20.3.1.2.5 α-Diazo-β-ketoamides

An intramolecular reaction of an unsaturated α-diazo-β-ketoamide was tested with several catalysts in progress toward the total synthesis of (±)-actinophyllic acid (see Section 4.20.4.2.1).[189]

4.20.3.1.2.6 3-Diazopyridine-2,6(1H,3H)-dione

3-Diazopyridine-2,6(1*H*,3*H*)-dione **87** reacted with styrene **10** in the presence of $Rh_2(OAc)_4$ **36**, leading to the corresponding cyclopropane with a low yield.[190]



87

4.20.3.1.3 Other disubstituted carbonyl diazo compounds

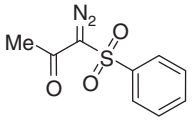
4.20.3.1.3.1 Nitrodiazoketones

Two reviews on the synthesis of nitrocyclopropanes, including the use of α-nitro-α-diazocarbonyl compounds in cyclopropanation reactions, have been published.[33,191] Nitrodiazoacetophenone **88** has been used in cyclopropanation reactions with some alkenes (styrene **10**, 2-methylpropene **89**, (*Z*)-2-butene **90**, and cyclohexene **49**) with variable yields (20–75%).[192] A number of nitrodiazoalkanones O_2NCN_2COR (R = Me, Pr, Bu^t, Ph) reacted with styrene **10** in the presence of $Rh_2(OAc)_4$ **36** with acceptable yields and variable *trans*/*cis*-stereoselectivities).[193]

The stereoselectivity of Rh-catalyzed Ar-CO-CN_2-NO_2 reactions can be affected by electronic effects of the aryl group. Thus, larger selectivities were found in the reactions catalyzed by an Rh chiral complex in the reactions involving electron-donor *p*-substituted phenyl groups (NMe_2, *trans*/*cis* = 1:99, 96% *ee*; CF_3, *trans*/*cis* = 30:70, 71% *ee*) and styrene **10**.[194]

4.20.3.1.3.2 Diazosulfonylketones

Two α-(arylsulfonyl)-α-sulfonylketones (1-(benzenesulfonyl)-1-diazopropan-2-one **91** and the related *p*-methyl-substituted analog **92**) have been used in $Rh_2(OAc)_4$ **36**-catalyzed cyclopropanation reactions of several allenes for synthetic purposes, though modest yields (up to 34%) have been obtained.[195]



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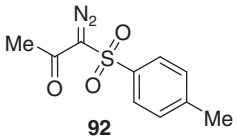


92

Good enantioselectivities (up to 93% *ee*) and yields (48–93%) have been achieved in intramolecular cyclopropanation reactions of some diazo(arylsulfonyl)alkenones using chiral Cu catalysts (see Section 4.20.4.2.1).[196]

4.20.3.1.3.3 Diazoketonitriles

High yields in catalyzed cyclopropanation reactions are usually obtained in catalyzed cyclopropanation reactions of α-diazo-β-diazoketonitriles because of the minimization of competing reactions, such as C–H insertion or carbene dimerization (see Section 4.20.4.1.1).[197] A number of cyanodiazoketones NC–CN_2–CO–R have been successfully used in cyclopropanation reactions with styrene derivatives and other alkenes using Rh catalysts.[180,198,199]

4.20.3.1.3.4 Nitrodiazoesters

Two reviews on the synthesis of nitrocyclopropanes, including the use of nitrodiazoacetic esters in cyclopropanation reactions, have been published.[33,191] Cyclopropanation reactions of diazonitroacetic esters are usually catalyzed by Rh complexes,[192,193,200–204] and also by copper[205] and cobalt[204] complexes. The *trans*/*cis*-stereoselectivities of cyclopropanation reactions of nitrodiazoacetates NO_2–CN_2–COOR in the presence of $Rh_2(OAc)_4$ **36** are strongly dependent on the R group hindrance (Me, 91:9; Et, 88:12; Pr^i, 75:25; Bu^t, 55:45).[193]

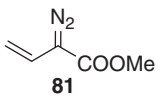
4.20.3.1.3.5 Cyanodiazoesters and cyanodiazoamides

Several cyanodiazoacetic esters NC–CN_2–COOR (R = Et,[182,206] Bu^t,[187,194,207] CF_3CH_2–)[182] have been used in catalyzed cyclopropanation reactions. Interestingly, both electron-rich and electron-deficient kinds of olefins can be used as substrates of cyclopropanation reactions by using cyanodiazoacetic esters (Et and Bu^t) and chiral Co-porphyrins as catalysts, with excellent diastereo- and enantioselectivities.[194]

Both *N*,*N*-dimethyl and *N*-isopropyl derivatives of cyanodiazoacetamide, NC-CN_2-$CONH_2$, were used in cyclopropenation reactions catalyzed by a Co catalyst with several 1-alkynes leading to high enantioselectivities.[207] In contrast, the use of the *N*,*N*-dimethyl derivative (as well as the *N*,*N*-diethyl analog) of cyanodiazoacetamide in cyclopropanation reactions of styrene catalyzed by some chiral Rh complexes led to very low enantioselectivities.[182] Interestingly, a spectacular increase in enantioselectivity was obtained by using the pyrrolidine-derived cyanodiazoacetamide, especially when triflamide was used as an additive (see Section 4.20.5.1.3).

4.20.3.1.3.6 Diazoalkenoic acid esters

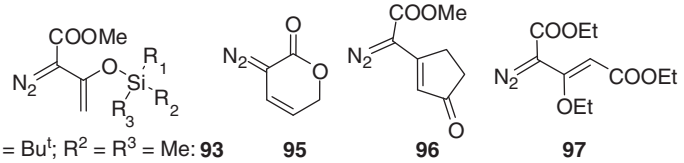
Several reviews involving vinyldiazoacetic esters, such as the chemistry of methyl 2-diazo-3-butenoate **81**,[208] and the use of rhodium-stabilized vinylcarbenoid intermediates in organic synthesis, have been published.[209,210]



81

Whereas low *trans*/*cis*-selectivities are usually found in cyclopropanation reactions of 2-nonsubstituted diazoacetic esters with styrene **10** (60:40 ratio for the $Rh_2(OAc)_4$ **36**-catalyzed reaction of ethyl diazoacetate **12** in dichloromethane at room temperature),[211] very high values are typically found in the analogous reactions of vinyldiazoacetates (see Section 4.20.4.1.5.2.2). Although these high selectivities have been usually attributed to the electron-donor properties of the vinyl group,[212] very good stereoselectivities have also been found in cyclopropanation reactions involving diazoesters bearing a further electron-withdrawing group in the α-position, such as ethoxycarbonylvinyl.[213]

Other diazoalkenoic esters used as carbenoid source in catalyzed reactions have been silyloxyvinyldiazoacetic esters (**93**,[176]**94**),[214] 3-diazo-3,6-dihydro-2*H*-pyran-2-one **95**,[215,216] methyl 2-diazo-2-(2-methyl-3-oxocyclopent-1-enyl)acetate **96**,[217] or diethyl (*E*)-2-ethoxy-4-diazopent-2-enedioate **97**.[218]



$R^1 = Bu^t$; $R^2 = R^3 = Me$: **93**
$R^1 = R^2 = R^3 = Pr^i$: **94**

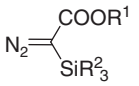
95 **96** **97**

4.20.3.1.3.7 Diazoalkynoic esters

High stereoselectitivites were found for the Rh_2(*S*-(*p*-dodecylphenylsulfonyl)prolinato (DOSP))$_4$ **42**-catalyzed reactions of 2-diazoalk-3-ynoic esters RC≡C–CN_2–COOMe (R=Et, Ph, Me_3Si) with a number of alkenes.[219]

4.20.3.1.3.8 Other diazoesters

Carbene and carbenoid chemistry of silyldiazoacetic esters has been reviewed.[220] A number of cyclopropanation reactions involving ethyl diazo(trimethylsilyl)acetate (R^1=Et, R^2=Me: **97**) have been reported. Thus, this reagent has been used in a cyclopropanation reaction of allyldimethylphenylsilane **98** with Cu/$CuSO_4$ catalysis with 82% yield.[221] A number of alkenes (1-hexene **7**, cyclohexene **49**, and styrene **10**) have undergone cyclopropanation reactions with ethyl diazo(trimethylsilyl)acetate **97** in the presence of the polymeric catalyst $[Ru_2(CO)_4(OAc)_2]_n$ **99** with good yields (54–89%).[222]



The reactivity of ethyl diazo(triethylsilyl)acetate(R^1=Et, R^2=Et: **100**), including cyclopropanation and cyclopropenation reactions, has been reviewed.[223] This reagent has been used in cyclopropanation reactions of styrene **10** catalyzed by chiral Rh complexes with approximately 70% yields and 82:18 *trans*/*cis*-diastereoselectivities.[224]

A number of silyldiazoacetic esters $R_3Si–CN_2–COOMe$ (R=Me, Et, Pr^i) were tested in reactions with styrene **10**, 1-hexene **7**, and cyclohexene **49** by using CuOTf **78**, $Rh_2(OAc)_4$ **36**, and $[Ru_2(CO)_4(OAc)_2]_n$ **99** catalysts.[225]

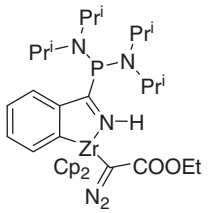
Both ethyl triethylsilyl- and (dimethylphenylsilyl)-diazoacetate have been reacted with styrene **10** in the presence of several Rh catalysts to afford the corresponding cyclopropanes with similar *trans*/*cis* ratios (82:18).[226,227]

3-Silylcyclopropene-3-carboxylic esters can be synthesized in acceptable yields (48–66%) by using silyldiazoacetic esters and alkynes (3-hexyne,[228] trimethylsilylacetylene,[229] a 3-substituted propyne)[158] in the presence of Rh catalysts.

Photochemical conditions have been tested for intramolecular cyclopropanation reactions of unsaturated silyldiazoacetic esters. Thus, a 2-silabicyclo[2.1.0]pentane has been synthesized through an intramolecular cyclopropanation of ethyl (allyldiisopropylsilyl)diazoacetate in photochemical conditions (68% yield), whereas no reaction was observed in thermal or Rh-catalytic conditions.[230] Instead, CuOTf **78** catalysis was preferred for the intramolecular cyclopropanation reactions of several substituted (alkenyloxy)silyldiazoacetic esters, photochemical conditions, and Rh catalysis leading to lower yields.[231]

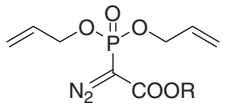
Only a few cases have been reported on the use of stannyl- and zirconiodiazoesters as carbenoid precursors. Thus, several stannyldiazoacetic esters R_3^1Sn-CN_2-$COOR^2$ (R^1=Me, R^2=Et; R^1=Bu, R^2=Et; R^1=Bu, $R^2=Bu^t$) have been tested in cyclopropanation reactions with styrenes and vinyl ethers catalyzed by the Cu–*N*-heterocyclic carbene (NHC) complex **101**.[232] These diazo compounds showed fair yields (50–71%) and high *trans*/*cis* ratios (up to ≥95:5) in the reactions with several *p*-substituted styrenes. Instead, no significant yields were obtained with other typical catalysts, such as $Rh_2(OAc)_4$ **36**, $Cu(OTf)_2$/$PhNHNH_2$, or $PdCl_2$.

The zirconiodiazoacetic ethyl ester **102** was separately reacted with methyl propiolate and diethyl butanedioate in the absence of a catalyst to yield the corresponding cyclopropenes.[233]



102

Several unsaturated (alkoxycarbonyl)diazophosphonic esters have been used in $Rh_2(OAc)_4$ **36**-catalyzed intramolecular reactions with excellent yields (88–97%) and diastereoselectivities depending on the alkoxycarbonyl group size (from 2.5:1 to 5.5:1) (see Section 4.20.4.2.1).[234–236]

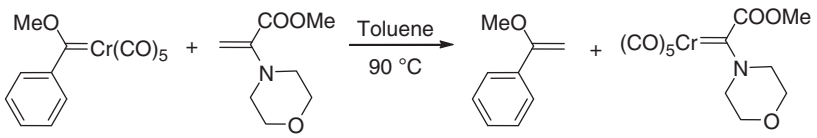


R = Me, Et, Bu^t, CH_2Ph, (*R*)-pantolactone

4.20.3.2 α-Amino-α,β-Unsaturated Carbonyl Compounds

Fischer carbene complexes (i.e., bearing π-donor groups on the carbene moiety) can be used as reactants for cyclopropanation reactions.[237] Interestingly, the combination of a π-donor (amino group) and a π-acceptor group (ester or amide) in Cr(0) carbene complexes has led to a new kind of ketocarbenoids, which are able to participate in cyclopropanation reactions.

Chromium ketocarbenoids bearing amino substituents can be obtained by metathesis from Fischer Cr–carbene complexes with α-amino-α,β-unsaturated carbonyl compounds (equation 11).[238] Several Cr-bound amino-ketocarbenes have been used in cyclopropanation reactions with different alkenes in refluxing toluene to yield the corresponding cyclopropanes with acceptable yields (30–70%).[239]



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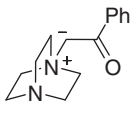
4.20.3.3 Ylides

The formation of ylides from the reactions between carbenes and carbenoids with heteroatom-bearing compounds has been reviewed.[2] Furthermore, the application of ylides to asymmetric cyclopropanation reactions has also been reviewed.[240] Ylides can be regarded as a safer alternative to the hazardous diazo compounds in cyclopropanation reactions.

4.20.3.3.1 Ammonium ylides

A number of achiral amines (trimethylamine, triethylenediamine, pyridine, and 1,4-diazabicyclo[2.2.2]octane (DABCO))[241] have been used in combination of α-halocarbonyl compounds for isolating or generating *in situ* ammonium ylides, which are able to induce cyclopropanation reactions with electron-deficient olefins (see Section 4.20.4.1.4.10). For example, *in situ*-generated phenacyl–DABCO ylide **105** reacts with *tert*-butyl acrylate[241] to yield the corresponding cyclopropanes.



105

However, a larger effort has been carried out for the use of asymmetric ammonium enolates in asymmetric cyclopropanation reactions (see Section 4.20.4.1.5.1).[242]

4.20.3.3.2 Arsonium ylides

The application of arsonium ylides in organic synthesis, including the cyclopropane formation, has been reviewed.[243] A number of ketone–arsorane derivatives, $Ph_3As^+CH^-COR$ (R = Me,[244] Ph, substituted phenyl,[71,245–248] 2-furanyl,[245,249] and 2-thiophenyl),[245,247,249,250] have been used in cyclopropanation reactions. In typical conditions, the corresponding arsonium bromide is reacted with electron-deficient olefins in the presence of Na_2CO_3, K_2CO_3, and KF (nonasymmetric variant), or an organocatalyst (asymmetric) (see Section 4.20.4.1.4.10).[71,246]

4.20.3.3.3 Sulfonium ylides

Sulfonium ylides are typically obtained from the reaction of an organic sulfide with an α-bromocarbonyl compound in the presence of a base (as K_2CO_3 or KOH) and, eventually, a phase-transfer catalyst (such as benzyltriethylammonium chloride (TEBAC)[251] or NBu_4Br).[252,253] Different reaction conditions have been employed for cyclopropanation reactions using sulfonium ylides.

$Ph_2S^+CH^-COOMe$ has been used in Cu-pentylacetylacetonate-catalyzed cyclopropanation reactions with variable yields: butyl vinyl ether **13** (92%), cyclohexene **49** (86%), 1-methylcyclohexene (84%), *trans*-2-octene (58%), styrene **10** (45%), 1-heptene (41%), and 2,3-dimethylbutene (4%).[254]

$Ph_2S^+CH^-COOEt$ has also been used in cyclopropanation reaction of styrene **10** with some Rh and Cu catalysts, although the results on yield and enantioselectivity are sligthly lower than the corresponding reactions of ethyl diazoacetate **12**.[255]

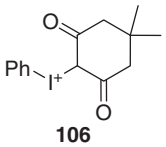
Sulfonium ylides have also been used in cyclopropanation reactions under photochemical conditions.[256] Thus, a number of sulfonium precursors of bis(methoxycarbonyl)carbene have been tested for the cyclopropanation reaction of cyclohexene **49** with modest results.

Cyclopropanation reactions of sulfonium ylides have been carried out in thermal conditions with electron-deficient olefins or fullerenes. A number of types of sulfonium ylides can be considered depending on the number and the nature of the substituents: aldehyde, ketone, amide, monoester, acylester, and diester.

4.20.3.3.4 Iodonium ylides

Iodonium ylides have been widely used for the cyclopropanation of electron-rich olefins in both nonasymmetric[255] and asymmetric[257] approaches using metal derivatives as catalysts.

The dimedone phenyliodonium derivative ((4,4-dimethyl-2,6-dioxocyclohexyl) (phenyl)iodonium **106**) has been used in cyclopropanation reactions with styrene **10** in moderate yields using $Cu_2(facam)_4$ (53% yield), $Rh_2(OAc)_4$ **36** (49% yield), and $Rh_2(nttl)_4$ **107** (37% yield).[175] These results constitute a significant improvement respective to the corresponding diazo compound, as the full styrene **10** polymerization was observed for the later reagent in the presence of a copper catalyst. However, a lower yield (18%) was obtained when the dimedone-derived ylide **106** was employed for the cyclopropanation reaction of 1-hexene **7** using $Rh_2(OAc)_4$ **36**) as a catalyst.



106

The methyl acetoacetate phenyliodonium ylide has been used in combination of $Rh_2(OAc)_4$ **36** for the cyclopropanation reactions with styrene **10**, *p*-methoxystyrene, and 1,1-diphenylethylene **108** in moderate yields (31–65%),[258] though the corresponding reaction of ethyl vinyl ether led to the quantitative formation of a dihydrofuran derivative. Instead, better yields for cyclopropenation reactions were obtained for phenylacetylene **14** (77%) and 1-pentyne (66%).

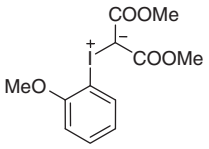
A large variety of ester-derived phenyliodonium ylides $PhI^+–C^-R^1–COOR^2$ (e.g., $R^1 = H$, $R^2 = Me$[112]; $R^1 = R^2 = Me$[259]; $R^1 = CF_3$, $R^2 = Et$[227]; $R^1 = Et_3Si$, $R^2 = Et$[227]; and $R^1 = NO_2$, $R^2 = Me$)[260,261] as well as Meldrum's acid derivative **109**[262] have also been used in cyclopropanation reactions. Other phenyliodonium ylides, such as that derived from 2,3-dihydro-3-oxobenzo[*b*]thiophene-1,1-dioxide, have also been used in catalyzed cyclopropanation reactions.[263]

Rh catalysts have been extensively used in cyclopropanation reactions of phenyliodonium ylides. For example, $Rh_2(esp)_2$ **71** has been used in CH_2Cl_2 in combination of the dimethyl malonate-derived phenyliodonium ylide for the cyclopropanation reactions of 1-hexene **7**, 4-phenylbut-1-ene, indene, allyl benzyl ether, *p*-substituted (H, F, Me, and OMe) styrenes, and some enynes (reacting on C=C bond).[264,265]

Copper catalysts (such as CuCl,[266] CuI,[178] $Cu(acac)_2$ **110**,[263] and CuOTf **78**)[267] have also been used in cyclopropanation reactions of iodonium ylides. Furthermore, Cu–box complexes have been used as catalystic cyclopropanation reactions using malonic[178] or nitroacetic derivatives of iodonium ylides.[261]

$AgSbF_6$ has been used as a catalyst for the reactions of styrene **10** with some malonic acid ester iodonium ylides.[178]

The dimethyl malonate-derived 2-methoxyphenyl iodonium ylide **111** is highly soluble in dichloromethane, chloroform, and acetone and has been applied in reactions with a number of alkenes and phenylacetylene **14** in the presence of $Rh_2(OAc)_4$ **36** to afford the corresponding three-membered rings with good yields (see also Section 4.20.5.1.2).[268]



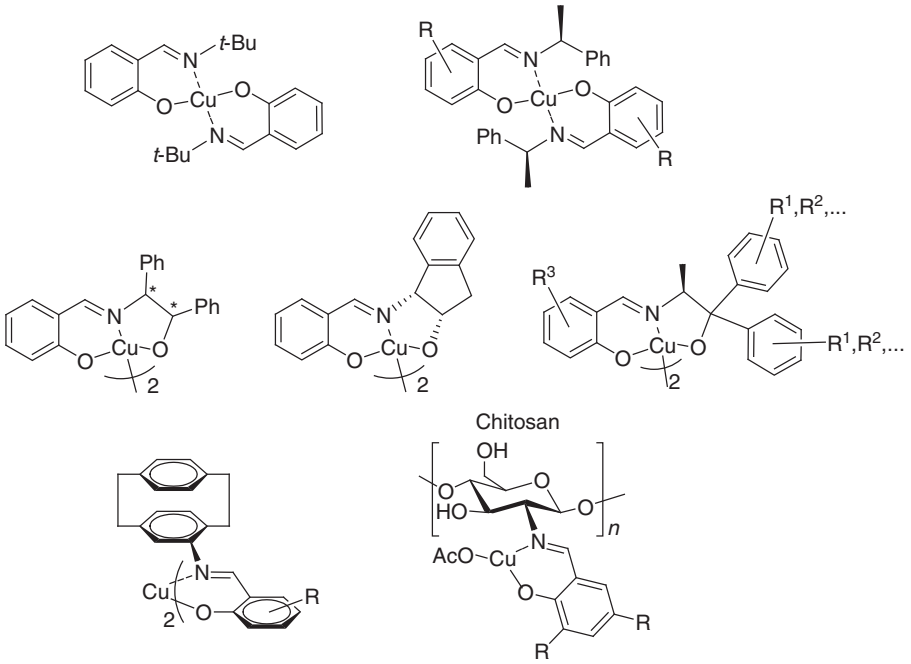
111

4.20.3.4 Metal Complexes

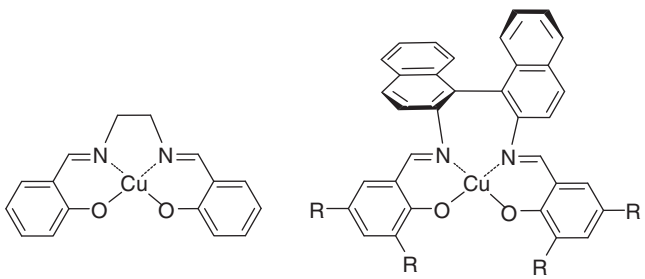
4.20.3.4.1 Copper complexes

Despite the increasing use of other metals, and especially rhodium, to stabilize ketocarbenes by formation of the corresponding metal–carbenoid intermediates, copper continues being one of the preferred metals for catalysis in cyclopropanation reactions. In many cases, metallic copper and simple copper salts, like $CuSO_4$ **112**,[269–283] or copper complexes, like $Cu(acac)_2$ **110**[284–292] are enough to efficiently promote either intra- or intermolecular cyclopropanation reactions. Some examples of using polyoxometalates as the copper counteranion have also been described.[293–295] However, in most cases, the use of more sophisticated ligands is preferred, in order to obtain the desired selectivity. A number of reviews dealing on copper-catalyzed cyclopropanation reactions have been published.[85,296] The different families of copper complexes described since 1989 will be briefly reviewed here.

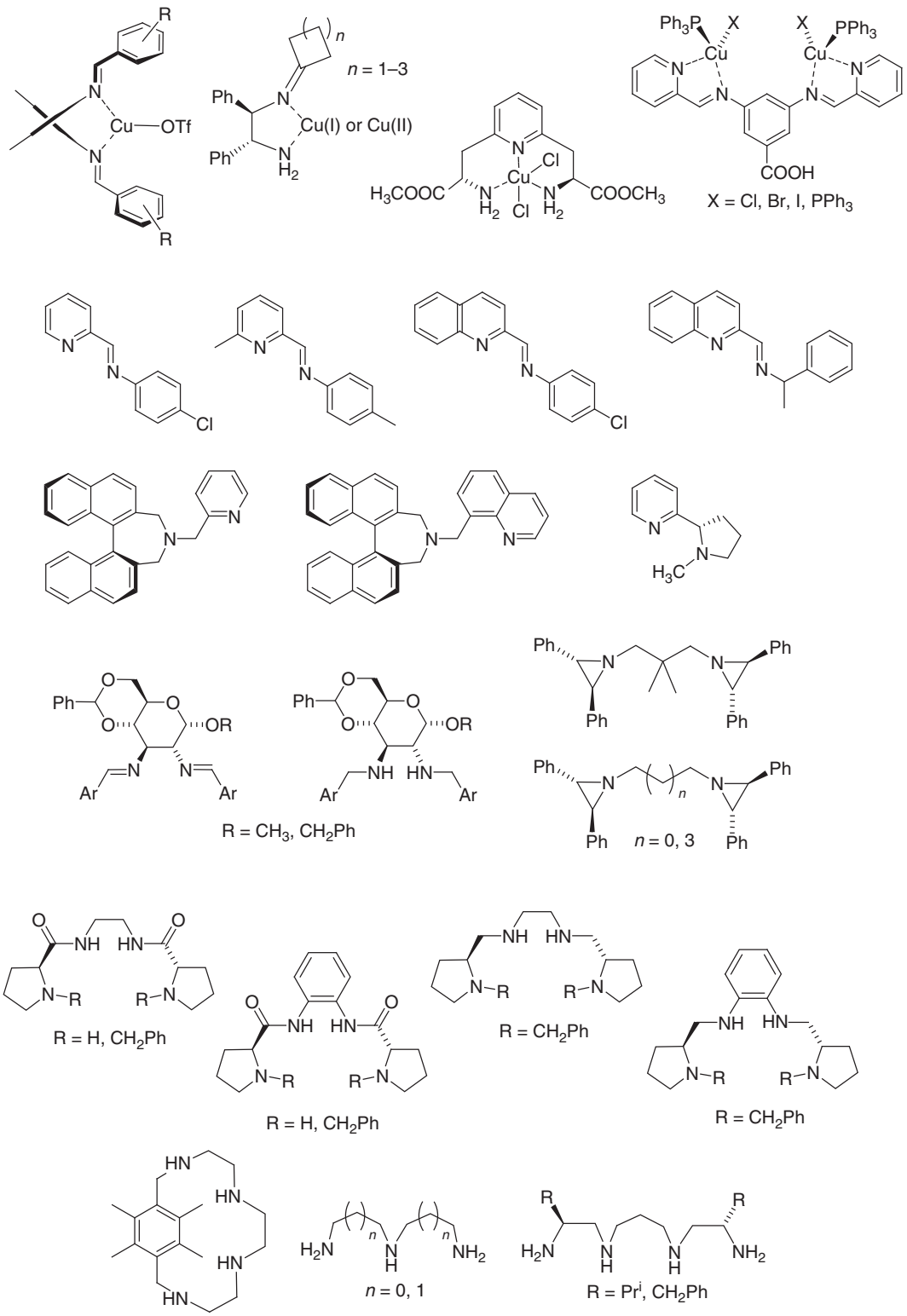
Salicylimino copper complexes, belonging to the copper–Schiff's base complex category, constitute a special class of catalyst, because the Nozaki's chiral version was the first enantioselective homogeneous catalyst ever described, and namely for a cyclopropanation reaction.[297] Since then, many variants of this catalyst, both nonchiral[298–307] and chiral,[308–318] usually named as the Aratani's catalyst, have been described.



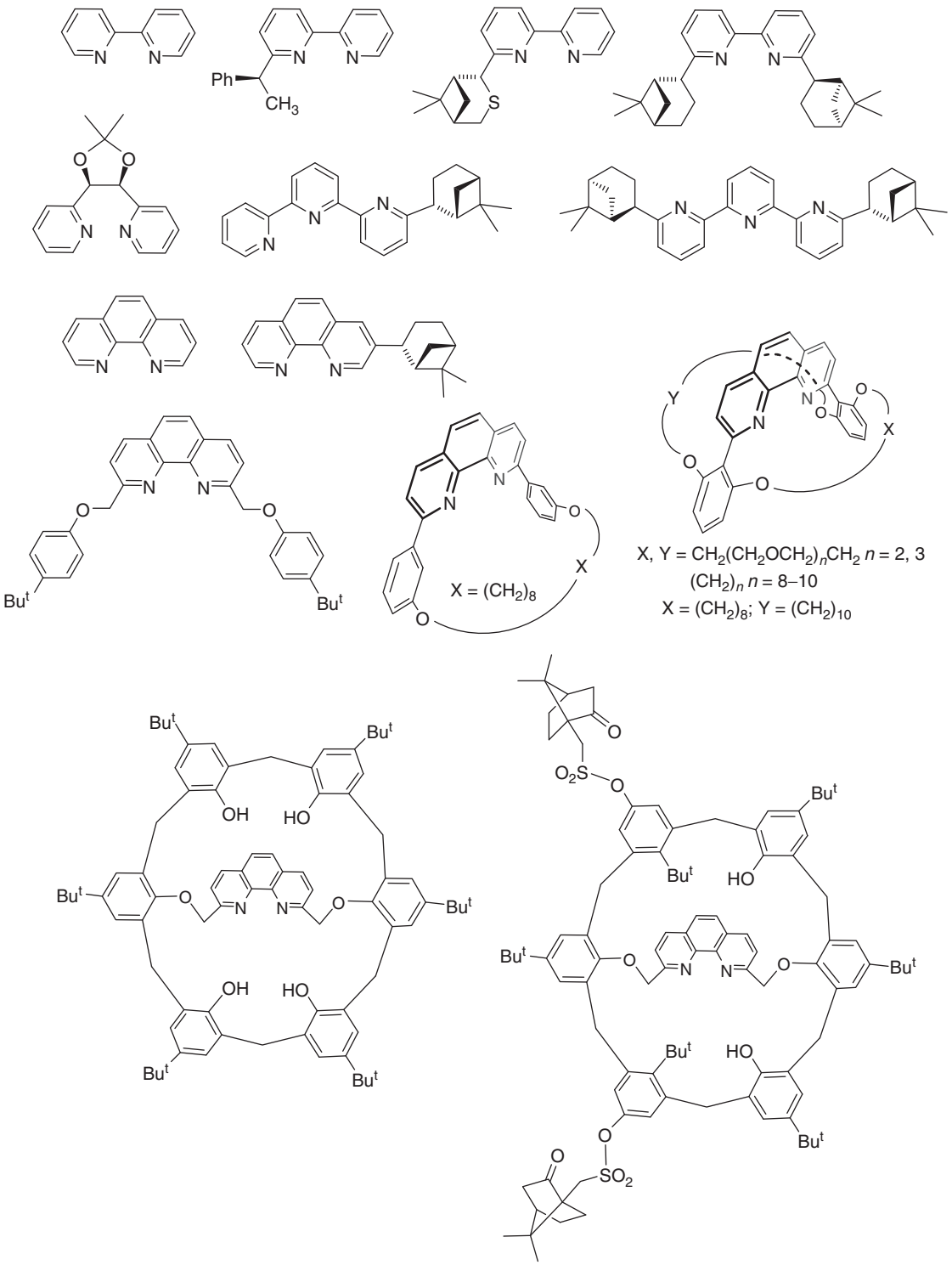
Structurally related to these are the salen–copper complexes, which have been much less studied in these kinds of reactions.



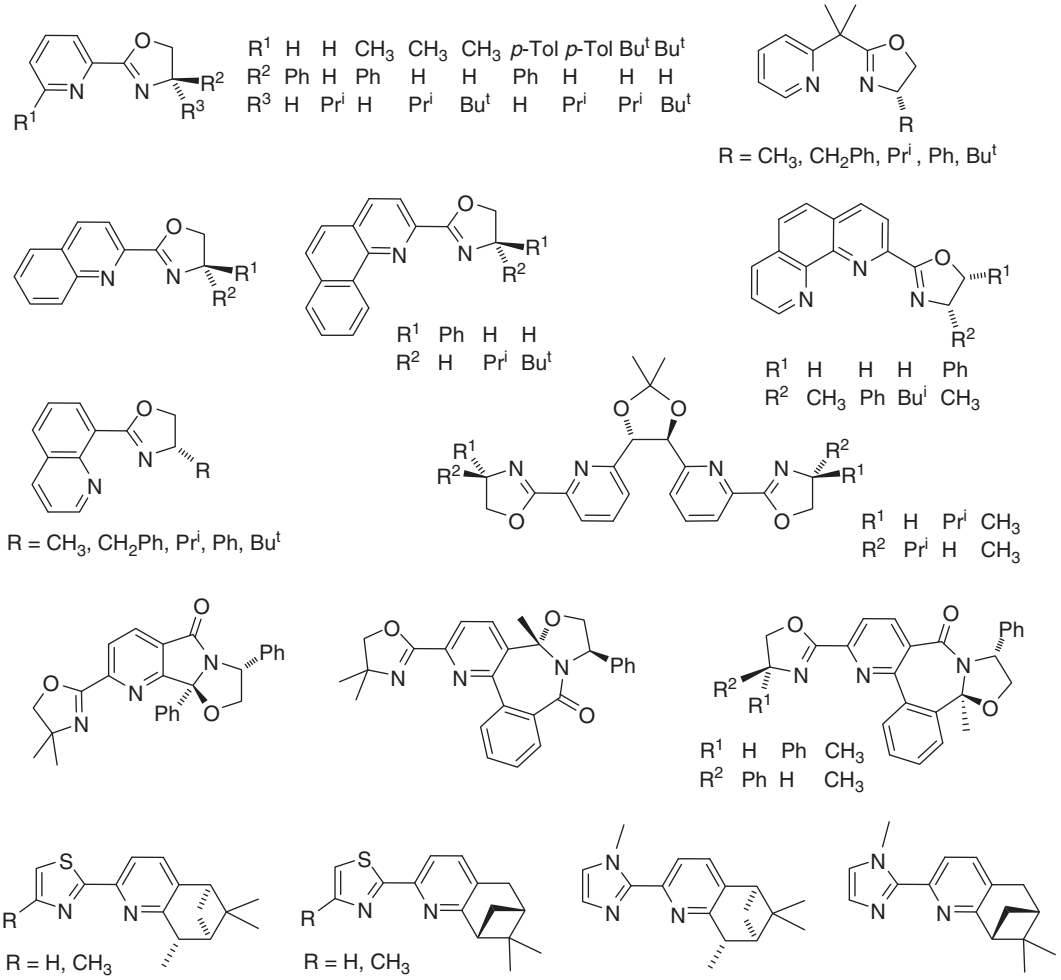
Copper–amine[319–322] and imine[321–325] complexes have also been used, including some polyazamacrocycles as ligands.[326–329]



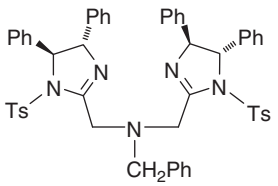
Other aza-ligands similar to copper–imine complexes are those based on azaheterocycles, such as pyridine, imidazoline, pyrazole, semicorrin, and oxazoline. Many examples have been published on the use of pyridine-based ligands, like bipyridines,[109,139,330–347] terpyridines,[90,348–353] and phenantrolines.[334,336,354–357]



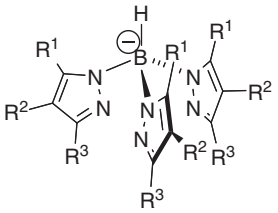
In addition, the use of mixed pyridine-heterocycle ligands, such as pyridylimidazoline[344] or pyridyloxazolines, has been described.[358–362]

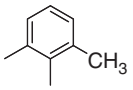
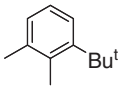
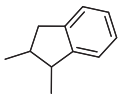


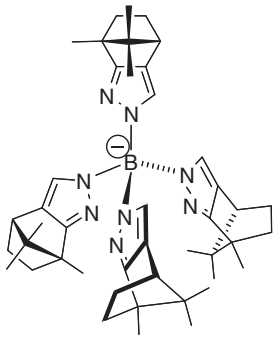
At least an example has been reported on the use of a bisimidazoline.[363]

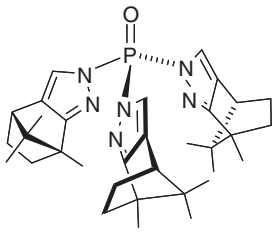


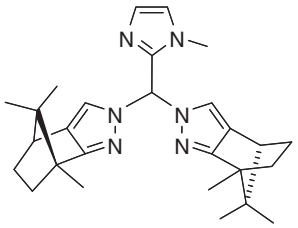
Polypyrazol ligands, and especially trispyrazolylborates, have also been widely used.[78,80,89,364–379]

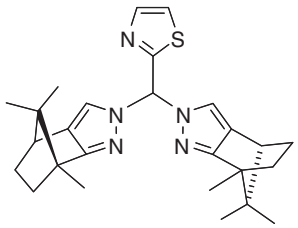


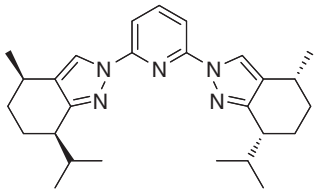
R^1	R^2	R^3
CH_3	H	CH_3
Bu^t	H	H
Bu^t	Br	H
Bu^n	H	CH_3
Pn^t	H	H
CH_2Ph	H	H
CH_2Ph	Ph	H
c-C_6H_{11}	H	H
c-C_6H_{11}	Br	H
Ph	H	H
Ph	H	CH_3
Ph	CH_3	H
Ph	Et	H
Ph	Pr^n	H
p-ClC_6H_4	H	H
p-$CH_3C_6H_4$	H	H
p-$CH_3OC_6H_4$	H	H
2,4,6-$(CH_3)_3C_6H_2$	H	H
1-Naphthyl	H	H
2-Naphthyl	H	H
1-Anthryl	H	H
Br	Br	Br
		H
		H
		H

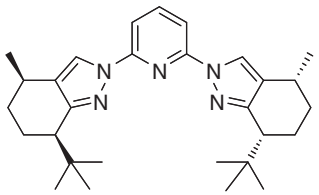


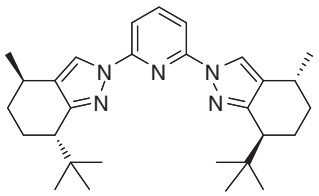




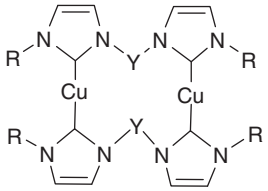






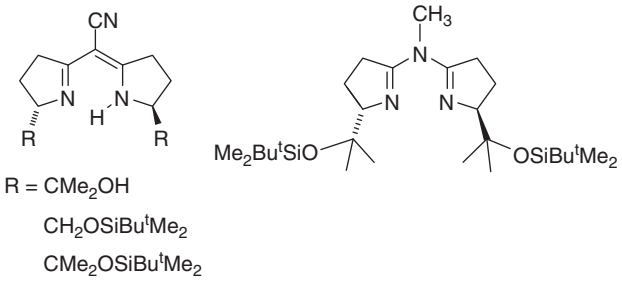


At least one example has been reported on the use of analogous ligands, but of NHC type.[380]



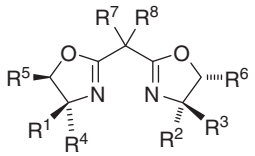
R = Me, Cy
Y = CH_2, CH_2CH_2, $CH_2CH_2CH_2$

Pfaltz described for the first time the use of semicorrin[381–384] and aza-semicorrin[385] as ligands in copper-catalyzed cyclopropanation reactions.



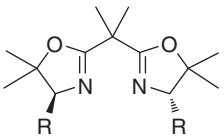
However, much more success has been reached with the bisoxazoline family of ligands,[382,384,386–409] first described by Masamune[74,410] and Evans,[142,411] and other related ligands of this family, such as bisoxazolylbiphenyls,[412–416] trisoxazolines,[152] borabisoxazolines,[417] and azabisoxazolines (**Table 3**).[418–421]

Table 3 Structure of bisoxazoline ligands described in the literature for cyclopropanation reactions[a]

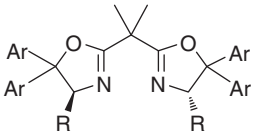


R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	*References*
Pr^i	Pr^i	H	H	H	H	H	H	74
Bu^t	Bu^t	H	H	H	H	H	H	74
CH_2Ph	CH_2Ph	H	H	H	H	H	H	74
Ph	Ph	H	H	H	H	H	H	74
H	H	Me	Me	Ph	Ph	H	H	410
H	H	Et	Et	H	H	H	H	
H	H	Et	Et	Bu^t	Bu^t	H	H	410
H	H	CH_2OH	CH_2OH	H	H	H	H	422
H	H	H	H	H	H	Me	Me	
Bu^t	H	H	H	H	H	Me	Me	406
Ph	H	H	H	H	H	Me	Me	406
Me	Me	H	H	H	H	Me	Me	406
Pr^i	Pr^i	H	H	H	H	Me	Me	142
Bu^t	Bu^t	H	H	H	H	Me	Me	142
Ph	Ph	H	H	H	H	Me	Me	423
Bu^t	Me	H	H	H	H	Me	Me	406
Bu^t	CH_2Ph	H	H	H	H	Me	Me	406
Bu^t	Ph	H	H	H	H	Me	Me	406
CH_2Ph	CH_2Ph	H	H	H	H	Me	Me	
Ph	H	H	Me	H	H	Me	Me	406
Ph	Ph	Me	Me	H	H	Me	Me	406
H	H	H	H	Ph	Ph	Me	Me	406
Ph	Ph	H	H	Ph	Ph	Me	Me	410
H	H	Ph	Ph	Ph	Ph	Me	Me	
Pr^i	Pr^i	H	H	H	H	Et	Et	196
CH_2Ph	CH_2Ph	H	H	H	H	Et	Et	196
Bu^t	Bu^t	H	H	H	H	$-CH_2CH_2-$		424

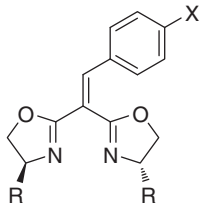
[a]Some ligands have been depicted as the enantiomers of those described in the original reference, for the sake of simplicity.



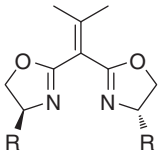
R = Ph, *o*-$MeOC_6H_4$, 1-naphtyl, 2-naphtyl



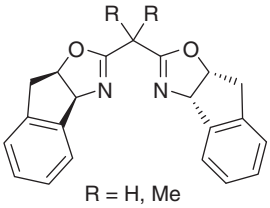
R = Pr^i, Bu^t, Ph, CH_2Ph
Ar = *p*-MeC_6H_4, 2-naphtyl



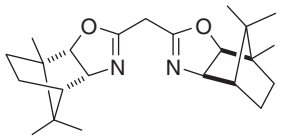
R = Pr^i, Bu^t, Ph, CH_2Ph
X = H, Cl, OMe

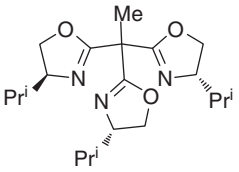


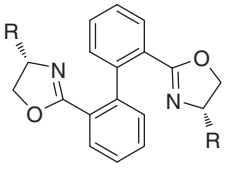
R = Pr^i, Bu^t, Ph, CH_2Ph



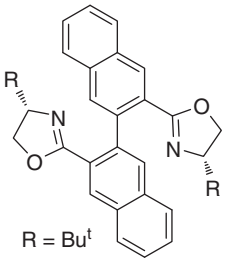
R = H, Me



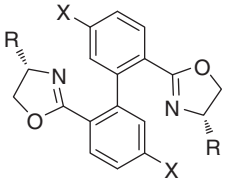




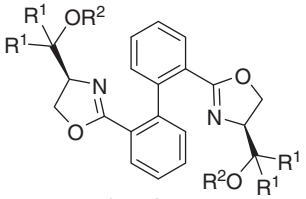
R = Pr^i, Bu^t



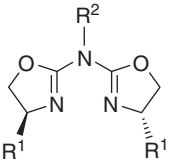
R = Bu^t



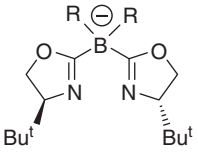
R = Pr^i, Bu^t
X = Cl, Ph



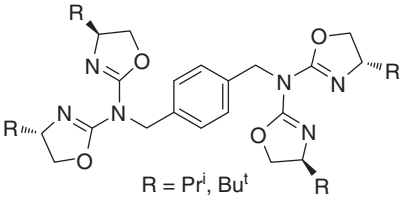
$R^1 = R^2 = H$
$R^1 = R^2 = Me$
$R^1 = R^2 = Et$



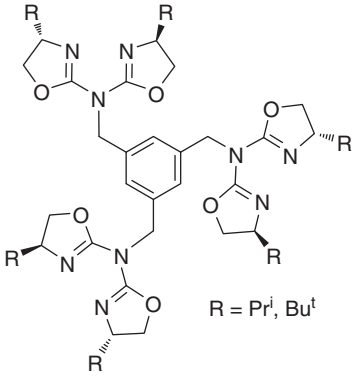
R^1= Pr^i, Bu^t, Ph
R^2= H, Me, CH_2Ph



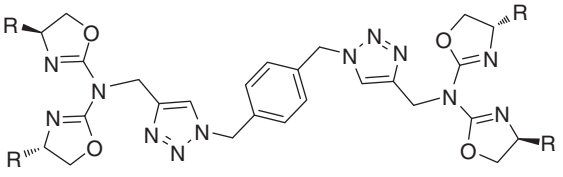
R = Me, Ar_F



R = Pr^i, Bu^t

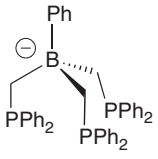


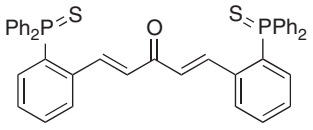
R = Pr^i, Bu^t

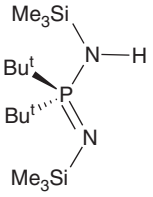


R = Pr^i, Bu^t

In contrast, the use of phosphorous-containing ligands is much more scarce.[82,364,425,426]





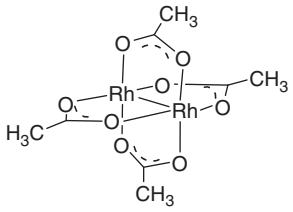


Finally the use of metal-organic frameworks (MOF) has also been recently described.[151,427,428]

4.20.3.4.2 Rhodium complexes

A brief review of the most important rhodium catalysts for carbene insertion reactions is considered here. A number of reviews devoted to Rh catalysis on cyclopropanation reactions have been published.[429–434] In addition, a number of reviews devoted to specific rhodium complexes (dirhodium tetraacetate,[118] dirhodium(II) tetraoctanoate,[435] dirhodium(II)tetrakis(trifluoroacetate),[436] dirhodium(II) tetrakis(perfluorobutanoate),[438] dirhodium(II) tetraacetamidate,[437] dirhodium(II) tetra(caprolactamate),[438] dirhodium(II) tetrakis(methyl 2-pyrrolidone-5-(*S*)-carboxylate),[438] dirhodium(II) tetrakis[(*R*)-2-oxoazetidine-4 (*S*)-carboxylate]),[439] Rh_2(5*R*-MEPY)$_4$, and Rh_2(5*S*-MEPY)$_4$,[440] typically used in cyclopropanation reactions, have been published. On the contrary, the use of donor/acceptor rhodium-stabilized carbenoids in a number of reactions, including cyclopropanation, has also been reviewed.[441]

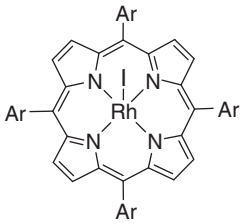
Among dirhodium compounds, dirhodium acetate **36** can be considered to be one of the most used transition-metal catalysts in organic reactions involving metal–carbenoid intermediates. Since the discovery of its catalytic activity in the early 1970s, a plethora of articles have been devoted to understand the mechanism and synthetic uses of this catalyst.[124,137,172,227,258,283,303,442–490]



36

Dirhodium acetate**36** is also important for being the inspiration and starting material for the development of new rhodium catalysts such as other rhodium carboxylates. These compounds can be easily obtained from the acetate precursor by ligand exchange reactions. The most frequently used are trifluoroacetate (TFA)[121]**113**, triphenylacetate (TPA) **114**, pivalate (piv) **115**, caprolactamate (cap) **116**, octanoate (oct)[491]**117**, and perfluorobutanoate (pfb) **118**. In some cases, tuning those carboxylate ligands may change the chemo or stereoselectivity of the reaction[485,489,492–500]

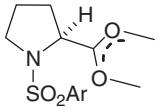
Among the wide range of ligands used with rhodium for ketocarbenes addition reactions, porphyrins appeared to be interesting for exhibiting an unusual propensity to provide mostly the *syn* diastereomer when bulky macrocycles are used.[501] Starting from the basic structure of Rh(TPPI) **119** described by Callot in 1980,[502] a great variety of ligands can be designed by modifying the aryl substituents.



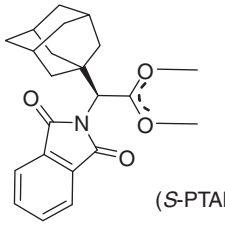
TPP: Ar = C_6H_5
TpFPP: Ar = C_6F_5
TTP: Ar = *p*-tolyl
TMP: Ar = mesityl

The design and use of chiral dirhodium(II) complexes as catalysts for asymmetric carbenoid reactions has been extensively reviewed.[503–505]

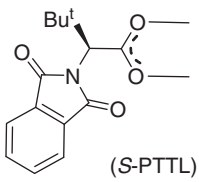
The first chiral rhodium complexes were based on carboxylate ligands. Amino acid derivatives such as prolinates[149,212,506–525] ((*S*-DOSP) **120** or (*S*-TBSP) **121**), glycinates, or *tert*-leucinates[177,178,180,199,227,526–531] such as ((*S*-PTAD) **122**, (*S*-PTTL) **123**, and (*S*-NTTL) **124**) are among the most used quiral carboxylate ligands. Some more sophisticated ligands such as rigid bridged prolinate ligand ((*S*-biTISP) **125**, (*S*-biTBSP) **126**, and (*S*-biDOSP) **127**)[532] or azanorbornanes[533] have also been described.



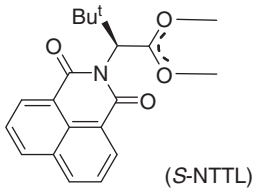
Ar = *p*-$C_{12}H_{25}{}^tC_6H_4$: *S*-DOSP **120**
Ar = *p*-$Bu^tC_6H_4$: *S*-TBSP **121**



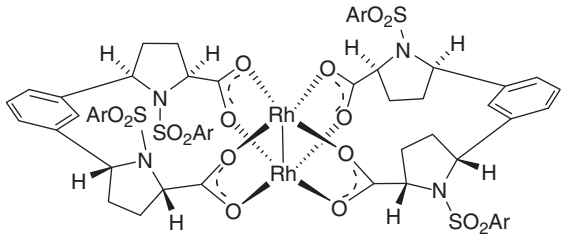
122



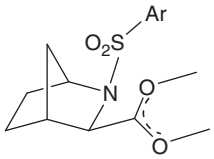
123

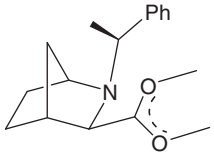


124

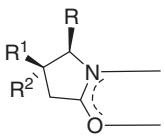


Ar = 2,3,4-triPr^{i}C$_6$H$_4$:Rh$_2$(*S*-biTISP)$_4$
Ar = *p*-Bu^{t}C$_6$H$_4$:Rh$_2$(*S*-biTBSP)$_4$
Ar = *p*-C$_{12}$H$_{25}$C$_6$H$_4$:Rh$_2$(*S*-biDOSP)$_4$

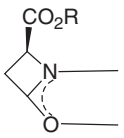




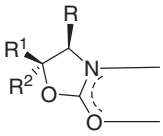
However by far, carboxyimidates have been the preferred ligands for the synthesis of chiral Rh catalysts.[534–539] A great variety of ligand structures have been designed, based on pyrrolidin-2-one, 2-oxazolidinone, *N*-acylimidazolidin-2-one, and 2-azetidinone moieties. These catalysts have structures much more rigid than their carboxylate counterparts, the rhodium atoms being closer to the chiral elements of the ligands.



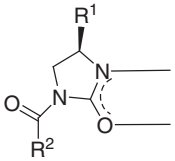
(5*S*)-MEPY (R=CO$_2$Me R^1=R^2=H)
(5*S*)-diFMEPY (R = CO$_2$Me R^1=R^2=H)
(5*S*)-DMAP (R = CONMe$_2$ R^1=R$^{2'}$=H)
(5*S*)-NEPY (R = CO$_2$CH$_2$CMe$_3$ R^1=R^2=H)
(5*S*)-ODPY (R = CO$_2$(CH$_2$)$_7$CH$_3$ R^1=R^2=H)



(4*S*)-MEAZ (R = Me)
(4*S*)-IBAZ (R = Bu^i)
(4*S*)-NEPAZ (R = Pn^{neo})
(4*S*)-BNAZ (R = PhCH$_2$)
(4*S*)-CHAZ (R = *c*-C$_6$H$_{11}$)
(4*S*,*S*/*R*)-MENTHAZ (R = *S*/*R*-menthyl)
(4*S*,*S*/*R*)-NAPHTHAZ (R = *S*/*R*-naphthylethyl)

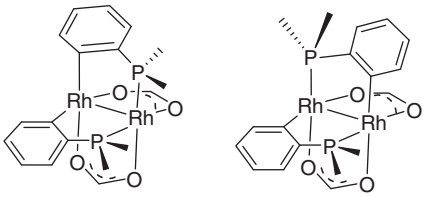


(4*S*)-IPOX (R=Pr^i R^1=R^2=H)
(4*S*)-PHOX (R = Ph R^1=R^2=H)
(4*S*)-BNOX (R = PhCH$_2$ R^1=R^2=H)
(4*S*)-MPOX (R = CH$_3$ R^1=R^2=H)
(4*S*)-MEOX (R = CO$_2$CH$_3$ R^1=R^2=H)
(4*S*)-THREOX (R = CO$_2$CH$_3$ R^1=H, R^2=CH$_3$)



(4*S*)-MACIM (R^1=R^2=Me)
(4*S*)-BACIM (R^1=Bu^i R^2=Me)
(4*S*)-MBOIM (R^1= Me R^2=Ph)
(4*S*)-MPAIM (R^1=Me R^2=PhCH$_2$)
(4*S*)-MPPIM (R^1=Me R^2=PhCH$_2$CH$_2$)
(4*S*)-MCHIM (R^1=Me R^2=cC$_6$H$_{11}$CH$_2$)
(4*S*)-MANIM (R^1=Me R^2=R,S-Ph(MeO)CH)
(4*S*)-EPPIM (R^1=Et R^2=PhCH$_2$CH$_2$)
(4*S*)-BPPIM (R^1=Bu R^2=PhCH$_2$CH$_2$)

Dirhodium(II) compounds bearing arylphosphine ligands, $Rh_2(O_2CR)_2(PC)_2$ (PC: *ortho*-metalated arylphosphine) **128**, have also received attention as chiral catalysts for ketocarbene reactions.[503,540,541] Two arrangements for the phosphine ligand are possible: *cis* head to tail or *cis* head to head, although the last ones show poor reactivity with diazo compounds.



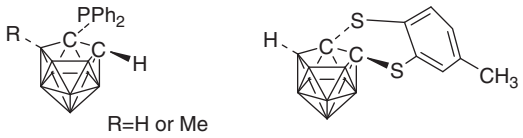
Head to head Head to tail

As head to tail compounds being inherently chiral, both enantiomers could be separated by column chromatography changing acetate ligands by chiral carboxylate ligands such as prolinate derivatives.[542]

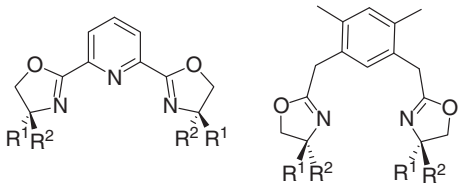
Introducing chirality by using chiral phospholane $Rh_2(O_2CR)_2(PC^*)_2$. ($PC^* = (2S,5S)$-2,5-dimethyl-1-phenylphospholane) **129** as starting material has also been explored.[543] In this way diastereomers could be isolated without the need of exchanging acetate ligands.

A great variety of phosphine-based catalysts have been synthesized by exchanging acetate ligands or modifying the substituents on the methalated ring. These substitutions provided great difference in activity and selectivity of the reaction.

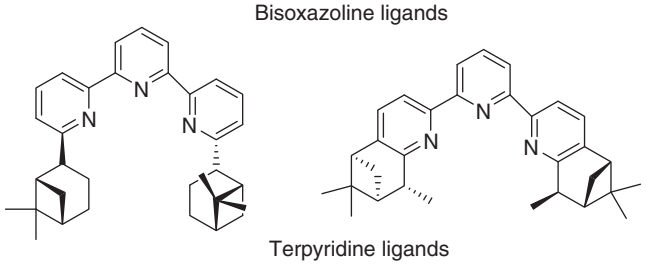
Some other compounds, such as carboranes,[544,545] bisoxazolines,[546] terpyridines,[348,350,352,378,547] or more recently *N*-heterocyclic iminocarbenes,[100,548,549] have been used in a minor extent as ligands in Rh complexes for ketocarbene addition reactions.



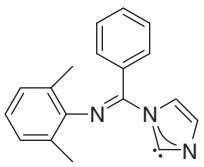
Carborane ligands



Bisoxazoline ligands

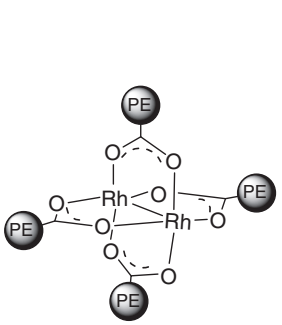


Terpyridine ligands

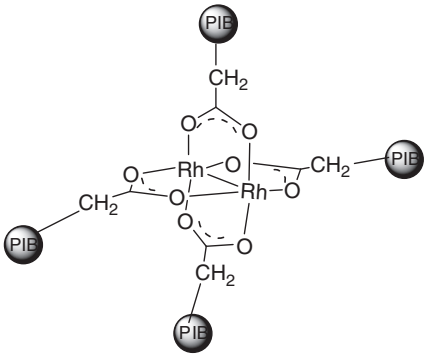


N-heterocyclic iminocarbene ligands

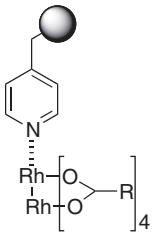
Some attempts have been made to design recoverable rhodium catalysts. In this way partially soluble complexes[550–552] have been used. The immobilization of the complexes onto polymers[553–558] or macropourous supports[559–561] has also been described, and biphasic systems have been applied such as the use of fluorinated ligands together with fluorinated solvents.[493,494]

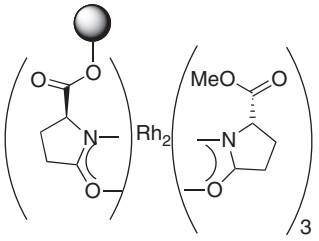


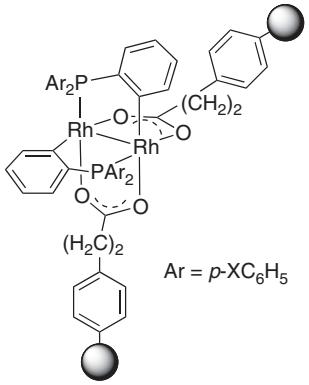
PE = Polyethylene



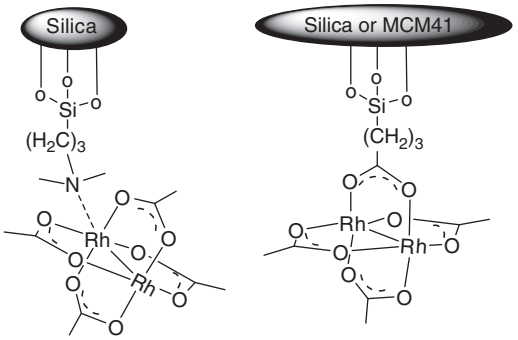
PIB = Polyisobutylene

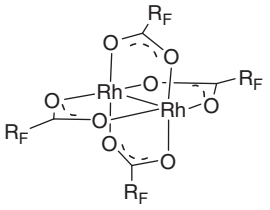






Ar = *p*-XC_6H_5



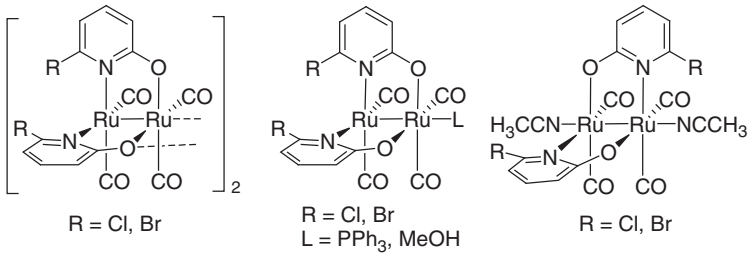


R_F=C_6H_4-4-C_6F_{13}
R_F=C_7F_{15}
R_F=C_6H_4-4-C_6F_{13}·$(CH_3CN)_2$

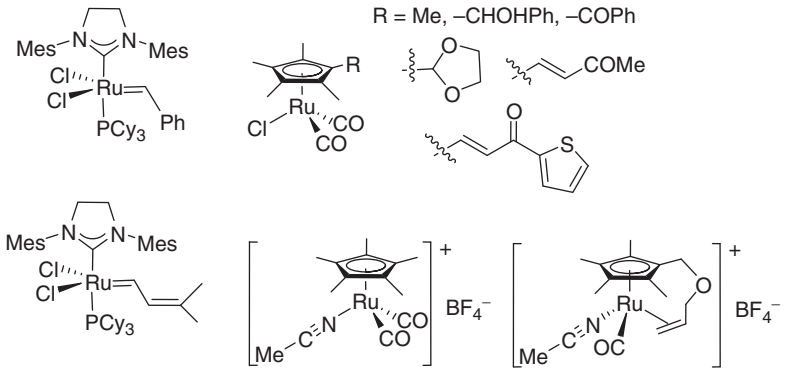
4.20.3.4.3 Ruthenium complexes

Ruthenium is probably the third most commonly used metal for cyclopropanations.[562] Cyclopropanation reactions catalyzed by Ru have been reviewed.[562–568] A large number of Ru complexes with simple mono- or bidentate ligands, such as

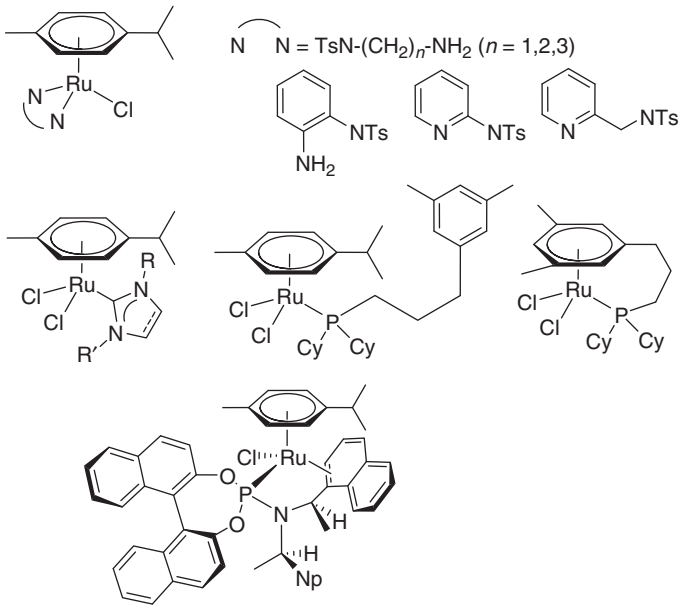
$RuCl_2(PPh_3)_2$,[569,570] $[Ru(CO)_2(OAc)]_n$,[222] dinuclear Ru-carboxylates as $[Ru_2(CO)_4(\mu\text{-}OOCCH_3)]_n$ or pyridonates,[571] and others have been used in cyclopropanation reactions.



Cp*RuCl(cod) (Cp* = pentamethylcyclopentadienyl) has been used for different tandem reactions including cyclopropanation.[572–574] The typical metathesis catalysts, with phosphine and carbene ligands, have been also used in tandem reactions.[575,576] The analogous $Cp^*RuCl(PPh_3)_2$ has been immobilized.[577] CpRu(II) complexes have been much more efficient than the analogous CpRu(IV) that lead to an unexpected competitive homologation reaction.[578]

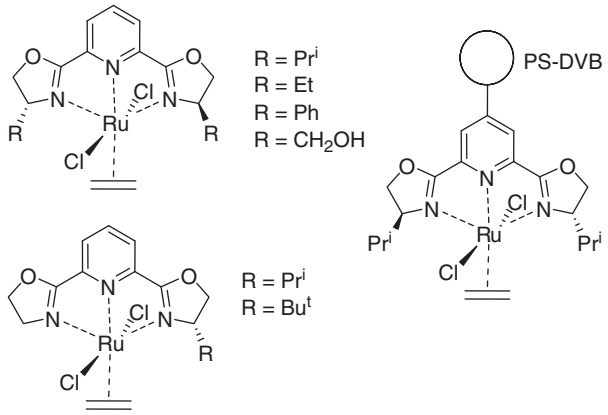


Ru(*p*-cymene) complexes have been also widely used, with additional ligands such as diamine-based ligands,[579] NHCs,[580,581] or phosphorous-based ligands, including a chiral monodentate phosphoramidite.[582–585]

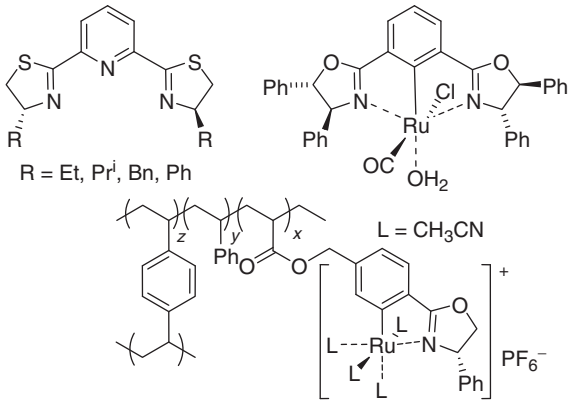


Chiral pyridine-2,6-bis(oxazoline)-$RuCl_2$(ethylene) complexes, developed by Nishiyama, have shown an enormous potential in enantioselective cyclopropanation reactions.[136,586–589] In fact several molecules of pharmacological interest have been prepared using this catalyst.[590–593] Another advantage of this kind of complex is the possibility of carrying out the cyclopropanation reaction in a protic medium[594] or even in the presence of water.[489] This complex has been immobilized in a reversible way by

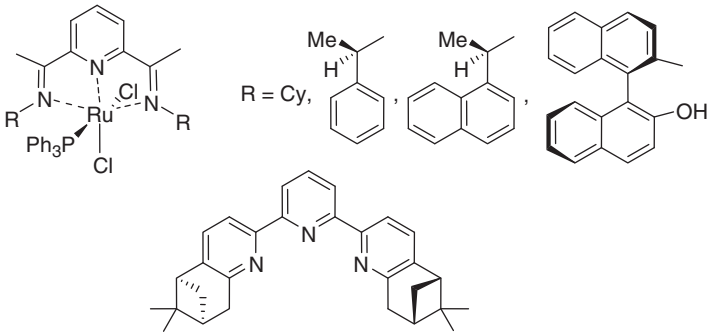
microencapsulation into polystyrene[595] or through formation of a covalent bond between C4 of the pyridine with an insoluble polymer.[596–598]



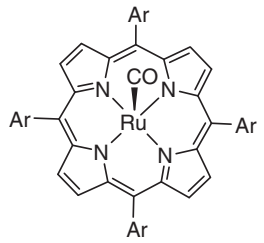
Analogous chiral ligands such as 2,6-bis(thiazolinyl)pyridines[599] or 1,3-bis(oxazolinyl)phenyl[600] have been also used. A phenyloxazoline ligand, without C_2 symmetry, has been immobilized on polystyrene-divinylbenzene and its Ru complex used in asymmetric inter and intramolecular cyclopropanations.[601]



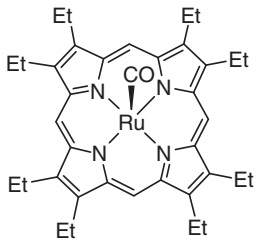
Ru complexes with other NNN tridentate ligands, such as pyridine-bisimino-$RuCl_2$[129,602] or terpyridine-$RuCl_2$[348] have been used in enantioselective cyclopropanation.



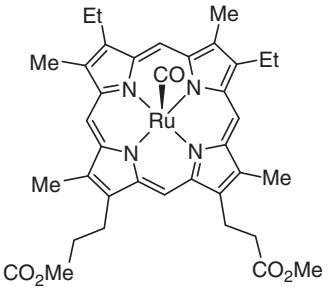
Porphyrin–Ru complexes are well-known catalysts for a large variety of reactions, including carbene transfer reactions.[567,568] Nonchiral porphyrin–Ru complexes,[603,604] as well as analogcomplexes with porphycene[603] and phthalocyanine[605] ligands have been reported as catalysts for cyclopropanation reactions. Porphyrines have been tagged with different groups, such as poly (ethylene glycol),[606] dendrimers,[607] or glucose,[608] to favor the separation of catalysts. Chiral substituents in porphyrines lead to Ru catalysts[92,171,609–611] that are able to promote enantioselective cyclopropanations. Those catalysts can be also immobilized[612] (e.g., by formation of polymers).[613,614]



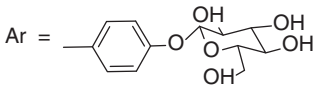
131: [Ru(TPP)(CO)]: Ar = Ph
[Ru(TMP)(CO)]: Ar = mesityl

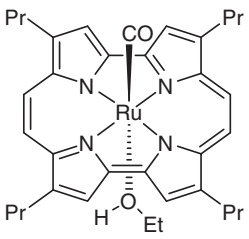


[Ru(OEP)(CO)]

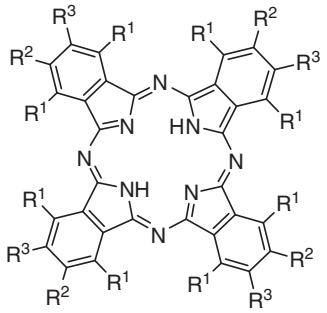


[Ru(MPIXDME)(CO)]

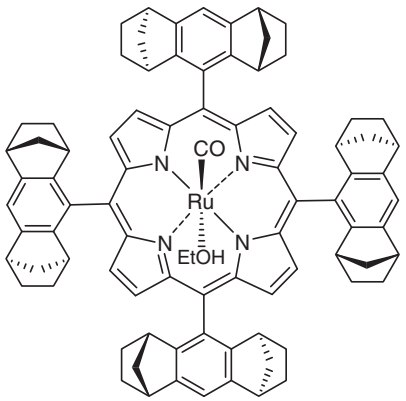


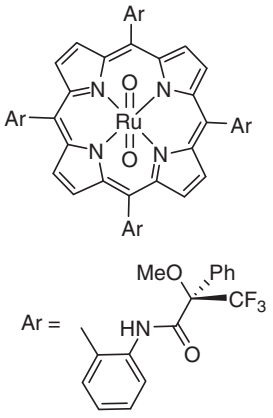


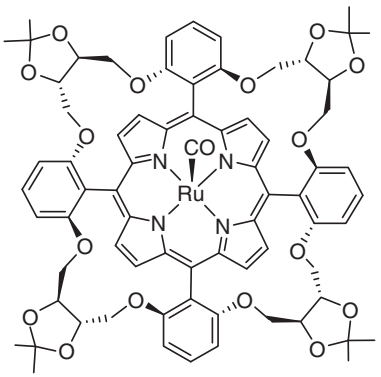
[Ru(TPrPc)(CO)(EtOH)]



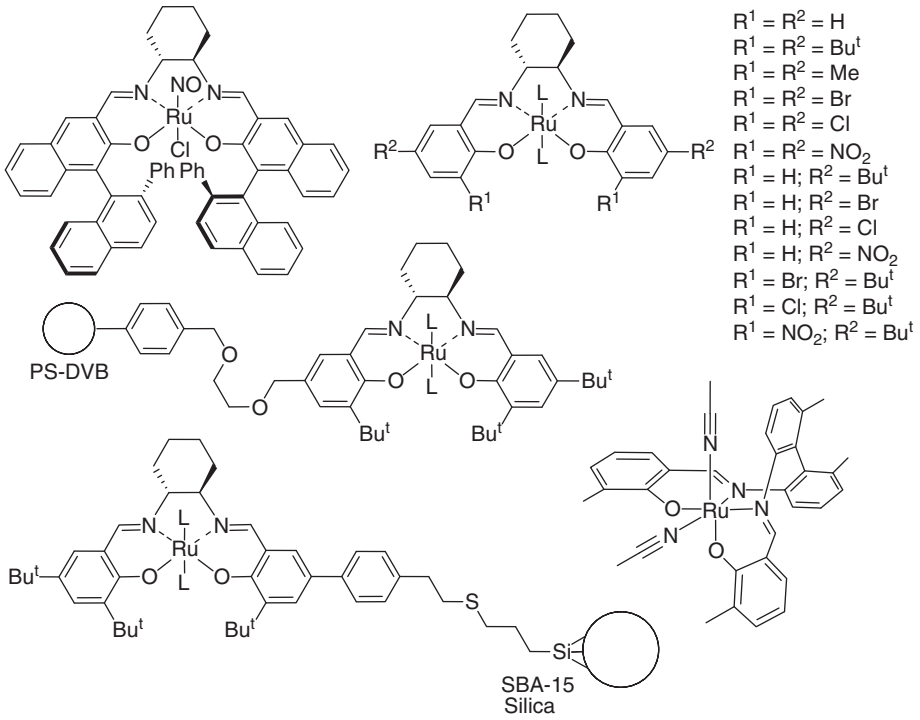
$R^1 = R^2 = R^3 = H$
$R^1 = R^2 = R^3 = Cl$
$R^1 = R^2 = R^3 = F$
$R^1 = R^2 = H$; $R^3 = Bu^t$
$R^1 = R^2 = H$; $R^3 = m\text{-}CF_3PhO–$



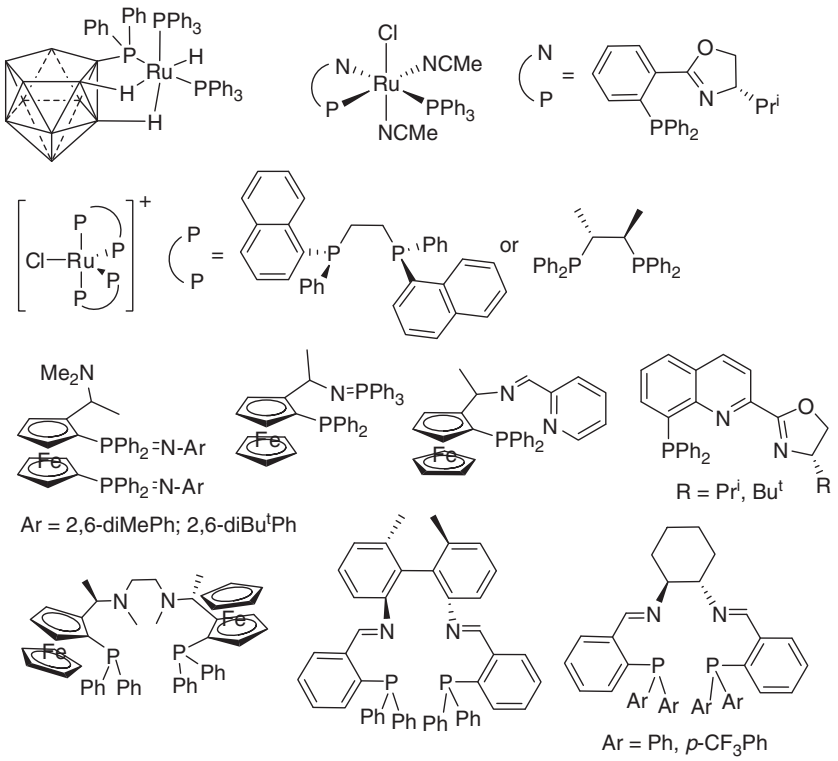




Chiral (salen)–Ru(II) complexes (salen = bis(salicylidene)ethylenediamine)[615–620] and one analog bis(salicylidene)biaryldiamine[621] have been described as highly efficient catalysts for enantioselective cyclopropanation. Even the nonchiral salen ligand has been used for this purpose by adding chiral sulfoxides as additional ligands.[622] Immobilization of salen–Ru by covalent grafting[623] on silica or polymer and by MOF formation[624] have also been described.

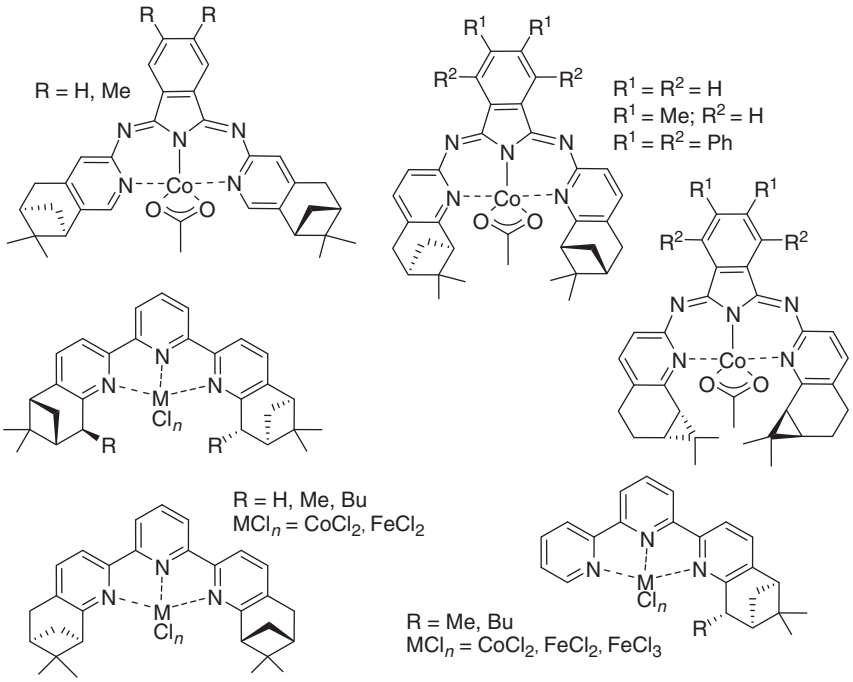


In the group of Ru complexes with polydentate phosphines several ligands can be included, such as a phosphinocarborane,[625] chiral diphosphines,[626] phosphinooxazoline,[627] iminophosphoranylferrocenes,[628] PNN-tridentate ligands,[629,630] and PNNP-tetradentate ligands with amino[631] and imino[632–634] groups.

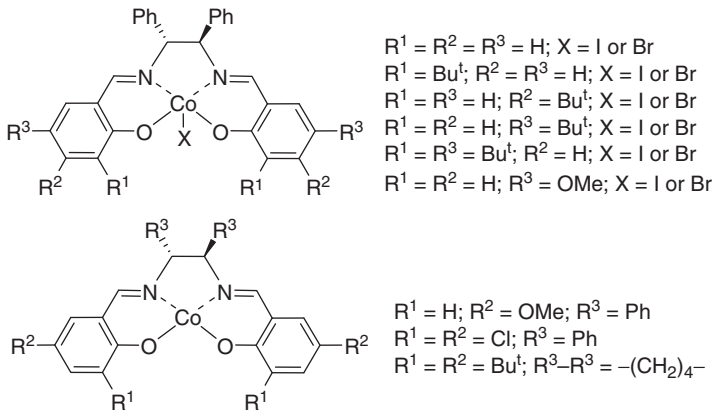


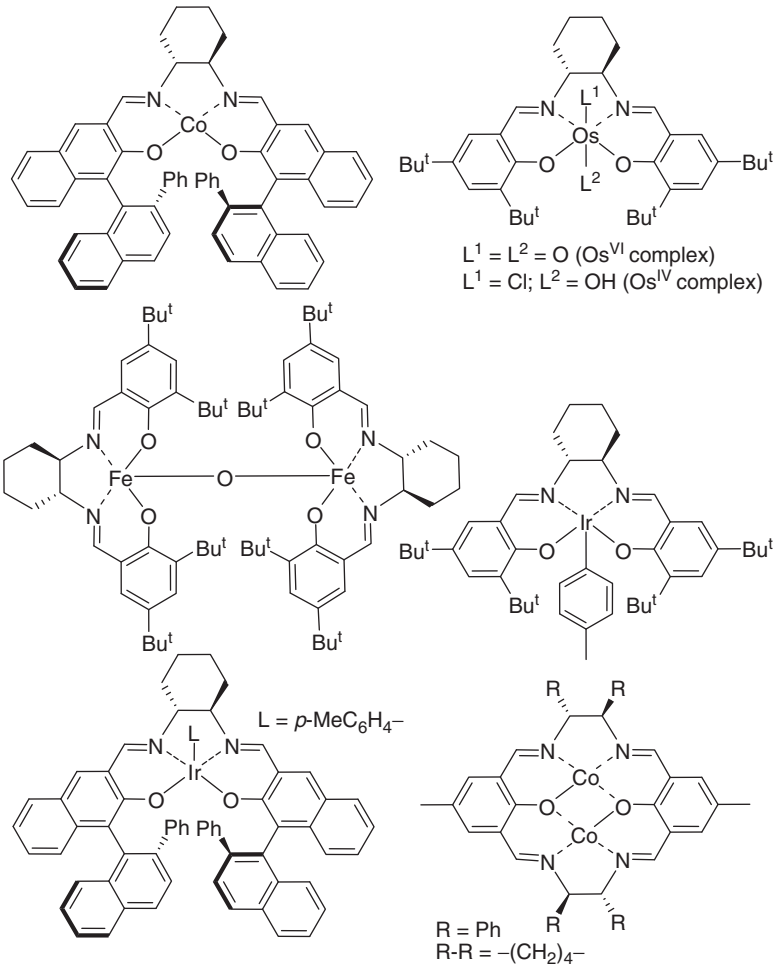
4.20.3.4.4 Cobalt, iron, osmium, and iridium complexes

Like rhodium and ruthenium, the other metals of groups 8 (Fe and Os) and 9 (Co and Ir) are also able to catalyze cyclopropanation reactions with diazo compounds. A number of reviews dealing with cyclopropanation reactions catalyzed by Co,[635] Fe,[636] and Os complexes have been published.[567] The use of simple ligands, such as $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(\text{tetrahydrofuran (THF)})]BF_4$,[637] $(Ph_3P)_3OsCl_2$,[570] and $[Os(p\text{-cymene})Cl_2]_2$, has been scarce.[638] Regarding enantioselective cyclopropanation, chiral-fluorinated diamines and diimines[639] as well as bis(pyridylimino)isoindoles[640] have been used for cobalt, whereas chiral terpyridines have been used for both cobalt and iron.[96] However, the most used ligands for these metals are ONNO (salen or β-ketoiminato) and NNNN (porphyrines).

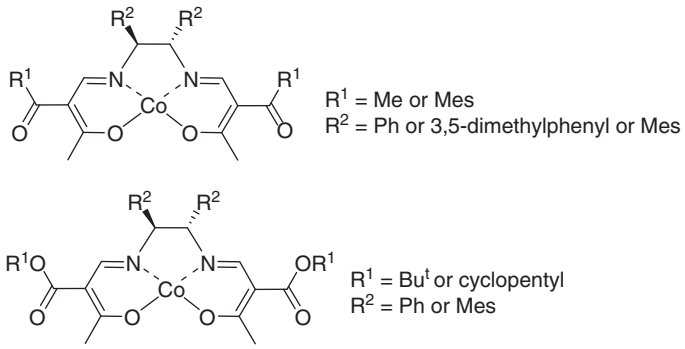


Chiral bis(salicylidene)ethylenediamines[618,641] of different structures and electronic properties have been used as ligands for cobalt,[132,489,642–644] iron,[645,646] osmium,[647] and iridium.[159,216,648,649] In the case of salen–Co, the catalyst has also been embedded into polymeric membranes.[650] A macrocyclic salen analog has been synthesized and the corresponding dinuclear LCo_2 has been tested in cyclopropanation.[651]

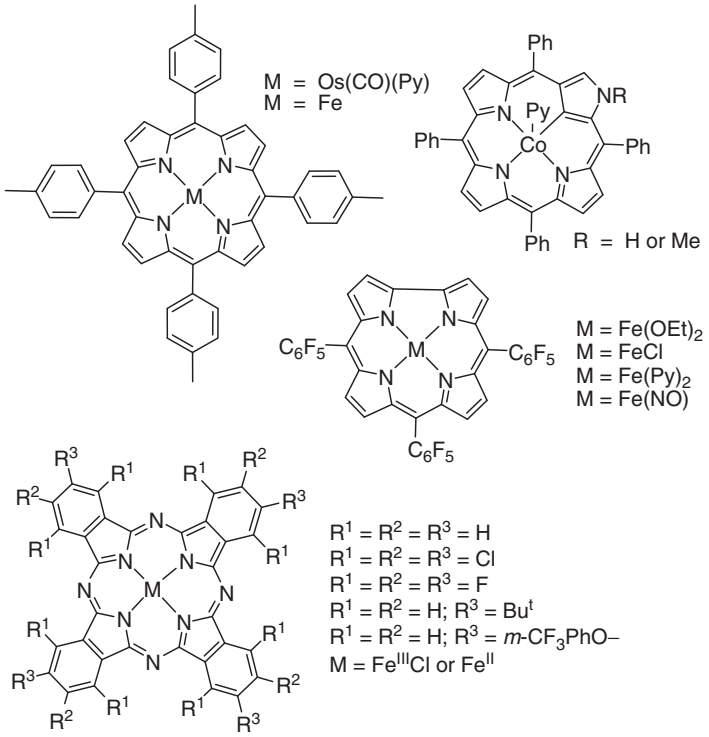




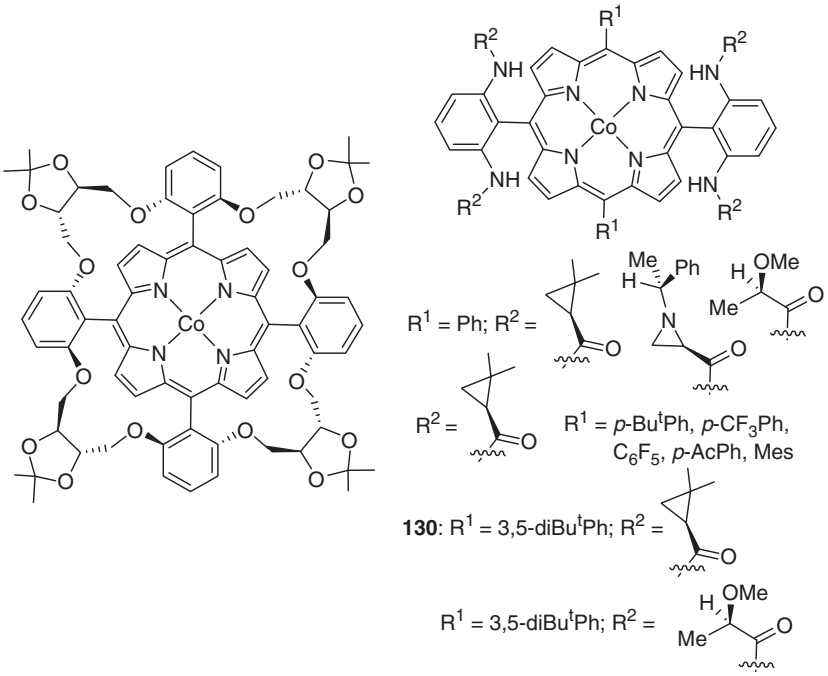
The structurally related chiral *β*-ketoimidato–Co complexes[652–654] have also been used for enantioselective cyclopropanation.

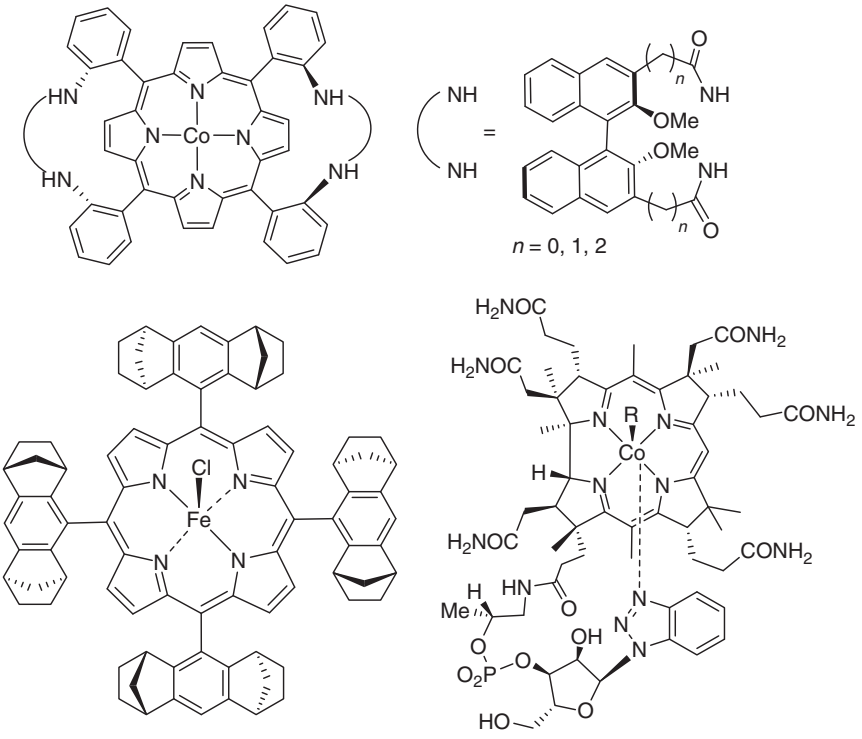


Nonchiral porphyrins have been mainly used to assess the feasibility of the cyclopropanation reaction catalyzed by Os,[655] and Fe[95] complexes including mechanistic studies,[128,656] or even the isolation of metal–carbene intermediates, such as those derived from porphyrin–Co[657] and porphyrin–Fe complexes.[658] Complexes with analogs of porphyrins, such as carboporphyrin–Co,[659] corrole–Fe,[660] or phthalocyanine–Fe[605] have been also tested.



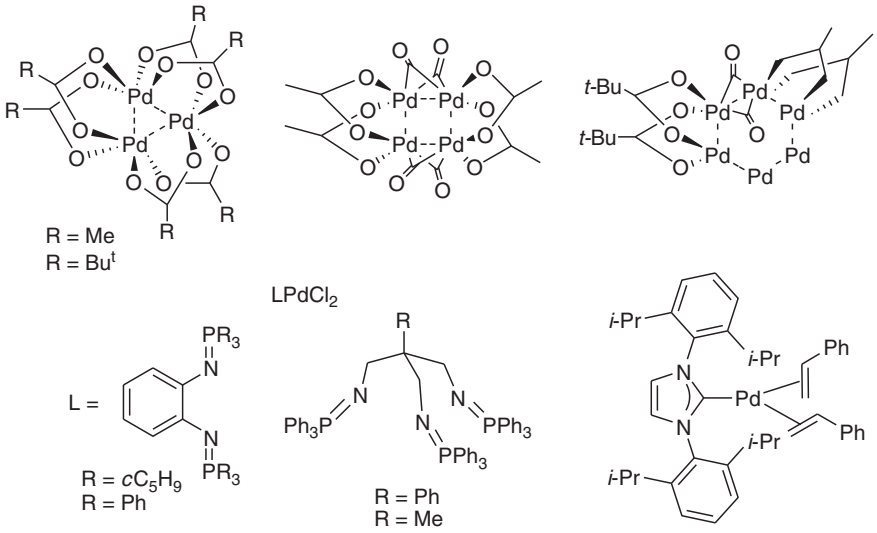
However, most of the research about the use of porphyrins as ligands for Co and Fe in cyclopropanation is devoted to the synthesis of chiral porphyrins and their application to enantioselective reactions. Substitution with 2,6-dialkoxyphenyl groups forming additional chiral macrocycles,[171,661] with chiral 2,6-dicarboxamidephenyl groups,[143,194,204,207,635,662–664] with binaphthyl-bridged phenyl groups,[665,666] or with a polycyclic octahydro-dimethylanthryl group (Halterman porphyrin)[667–669] are among the most successful examples, together with the use of a vitamin B_{12} derivative.[670]





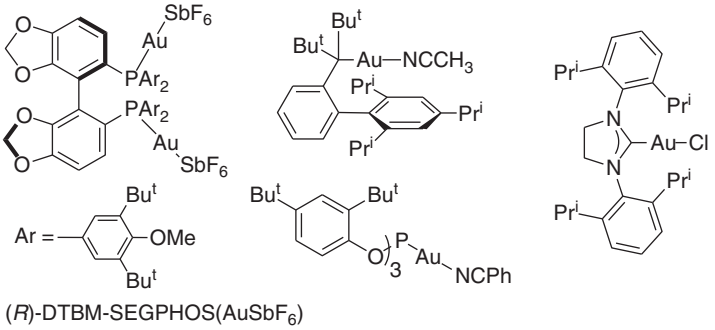
4.20.3.4.5 Palladium and platinum complexes

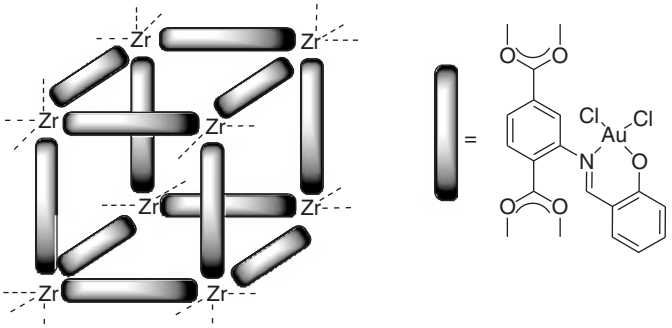
Palladium (II) acetate has been widely used as catalyst for cyclopropanations involving highly reactive diazo compounds,[173,300,308,488,671–674] such as diazomethane.[675,676] The analogous palladium (II) pivalate, with triangular Pd_3 core, the palladium-carbonyl acetate, with square Pd_4 core, and the palladium–carbonyl pivalate, with hexagonal Pd_6 core, have shown similar performance for cyclopropanations with ethyl diazoacetate **12**.[677] Palladium-catalyzed cyclopropanation reactions of diazoesters have been reviewed.[675,678] Other simple palladium complexes used as catalysts are $PdCl_2(PhCN)_2$,[679] $Pd(PPh_3)_4$,[76] complexes of $PdCl_2$ with diiminophosphoranes and triiminophosphoranes,[680] and NHC–Pd(0).[99] Platinum catalysts have been less commonly used, although different salts and complexes, such as $Pt(PPh_3)_4$, PtX_2 (Cl, Br, and I), PtX_4 (Cl and Br), L_2PtCl_2 (L=cyclohexene, benzonitrile, pyridine, and PPh_3) and $(NH_3)_2PtI_2$, have shown their activity.[681]



4.20.3.4.6 Silver and gold complexes

The reactivity of silver carbenoids has been reviewed.[682] Simple silver salts, such as $AgSbF_6$[150] or AgOTf,[155] in large amounts (10–15% catalyst) promote cyclopropanation reactions with diazo compounds. Gold–carbene intermediates can be generated from alkynes by using either $AuBr_3$[683] or phosphine–Au(I) cationic complexes,[684] such as $Ph_3PAuSbF_6$ or (*R*)-(4*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl] bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (DTBM-SEGPHOS)$(AuSbF_6)_2$. Diazo compounds can be activated with Au(I) complexes containing either phosphorous-based or NHC ligands.[685] Gold nanoparticles prepared from $NaAuCl_4$ or $KAu(CN)_2$ in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) ionic liquid are recoverable catalysts for cyclopropanation with ethyl diazoacetate **12**.[686] A salicylideneimino–gold (III) complex has been immobilized on a Zr-terephthalate MOF.[151]

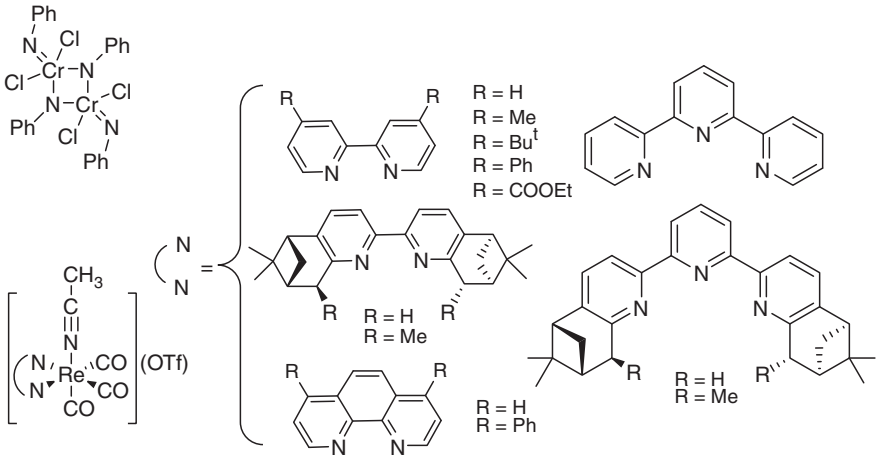




4.20.3.4.7 Chromium, rhenium, and molybdenum complexes

Chromium–carbene complexes are well-known reagents, but examples of chromium catalysts for carbene transfer are rather scarce. The most used catalyst is pentacarbonyl(η^2-*cis*-cyclooctene)chromium (0),[687–689] although bis(imido)chromium (VI) complexes[690] have been also tested.

With regard to rhenium, methyltrioxorhenium (MTO) is able to transfer carbenes to alkenes,[691] as well as [ReL$(CO)_3(CH_3CN)$](OTf) complexes,[692] where L is a 2,2′-bipyridine, phenanthroline or terpyridine, including some examples of chiral ligands.



$Mo(CO)_6$ has been used as a catalyst in the reaction between *β,β*-dinitrostyrene and diazoacetophenone **67** to generate the corresponding cyclopropane with a 70% yield.[693]

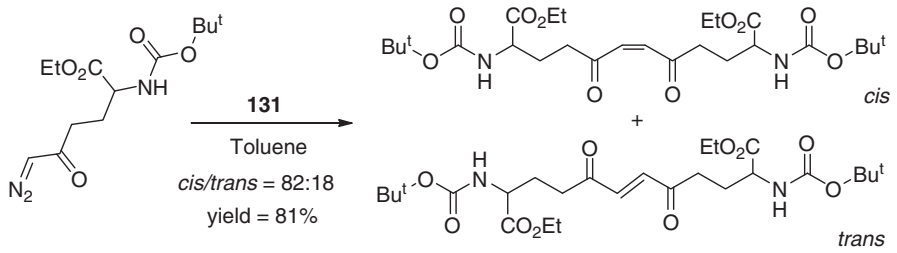
4.20.4 Addition of Ketocarbenoids to Alkenes

4.20.4.1 Intermolecular Reactions

4.20.4.1.1 Competing reactions

4.20.4.1.1.1 Dimerization of the diazo compound

The metal carbenoid complex can react with a free diazo compound molecule, leading usually to an alkene. A typical example is the formation of diethyl fumarate **60** and maleate in the reactions with ethyl diazoacetate. This side reaction can be minimized by using an excess of substrate and/or by slow addition of the diazo compound, and the effectiveness depends on the reactivity of the cyclopropanation substrate and on the nature of the catalyst.[680,694] The fumarate/maleate ratio is also controlled by the type of catalyst, with a remarkably high maleate selectivity with some Ru[589] or Fe[637] catalysts, although an important effect of the concentration of diazo compound and catalyst has been described for $RuCl_2(PPh_3)_3$.[695] This selectivity has been used to synthesize a dimer of the antiobiotic *N,O*-diprotected 6-diazo-5-oxo-*L*-norleucine using the Ru-complex (TPP)Ru(CO) **131** as a catalyst.[696]



(12)

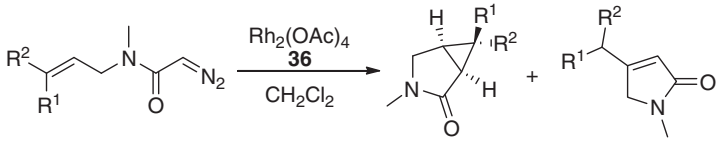
In principle, the suitable design of the catalyst could also inhibit this reaction, as demonstrated in the case of IPrCuCl [IPr: 1,3-bis(diisopropylphenyl)-imidazole-2-ylidene].[697] The nature of the metal is also of great importance. Complexes of Co and Fe with a D_2-symmetrical porphyrin have shown a lower activity for dimerization in the case of Co, whereas the addition of DMAP (4-dimethylaminopyridine) can significantly reduce the dimerization activity of the Fe complex.[663,664]

However, this reaction has been used in mechanistic studies to attempt isolating or detecting the metal–carbenoid complex, as, for example, in the case of Co(TPP) complex.[657]

4.20.4.1.1.2 Olefin metathesis and homologation

The formation of metallacyclobutanes with Ru catalysts seems to be the origin for the competitive metathesis[698,699] and homologation (formal insertion into the vinylic C–H bond)[578,700] products. The presence of titanocene or Ti-half-sandwich moieties in Ru–Ti heterobimetallic catalysts inhibits the metathesis pathway.[701]

The intramolecular cyclopropanation catalyzed by $Rh_2(OAc)_4$ **36** can compete with a sort of homologation, in fact an electrophilic addition of the meta–carbene to the double bond, and then migration of the double bond to be conjugated to the carbonyl group.[702]

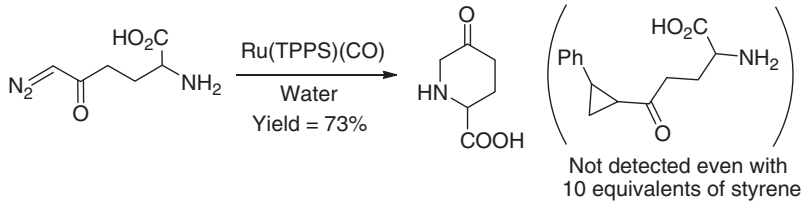


$R^1 = R^2 = Me$	70% yield	82:18
$R^1 = H, R^2 = Pr^n$	60% yield	97:1
$R^1 = Pr^n, R^2 = H$	54% yield	87:13

(13)

4.20.4.1.1.3 Carbene insertion reactions

Insertions into O–H and N–H groups are in general easier than cyclopropanation and favorably compete with it.[703] One example is the unprotected 6-diazo-5-oxo-*L*-norleucine that, even in the presence of a large excess of styrene, is able to produce the Ru-catalyzed intramolecular insertion into the N–H bond.[696]

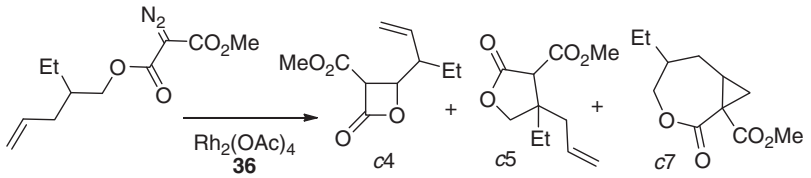


(14)

The case of C–H insertions[704–706] is completely different. A good number of studies have been published dealing with the tuning of the cyclopropanation/insertion ratio in Rh-catalyzed intramolecular reactions.[496,497,707,708] One example is the variation of products ratio by changing the reaction conditions (temperature and solvent) or ligand in the intramolecular reaction of diazomalonates.[500] In the case of Cu-catalyzed intramolecular reactions, the role of the ligand is also important, as demonstrated by the preference for cyclopropanation in the synthesis of 12β-hydroxy C_{20}-gibberellins using bis(*N*-*tert*-butylsalicylaldiminato) copper (II) **132,** whereas $Cu(acac)_2$ **110** favored the insertion into the 2α-C–H bond (Table 4).[301]

Table 4 Competitive Rh-catalyzed intramolecular cyclopropanation and C–H insertion reactions

Catalyst	*Solvent*	*Temperature (°C)*	*Combined yield (%)*	*Selectivity (%)*		
				c4	*c5*	*c7*
$Rh_2(OAc)_4$ **36**	CH_2Cl_2	r.t.	92	11	55	34
	Benzene	r.t.	66	<1	21	79
	Benzene	80	88	8	28	64
$Rh_2(piv)_4$ **86**	CH_2Cl_2	r.t.	88	6	17	76
	Benzene	r.t.	93	9	13	71
$Rh_2(pfb)_4$ **384**	CH_2Cl_2	r.t.	76	2	4	94



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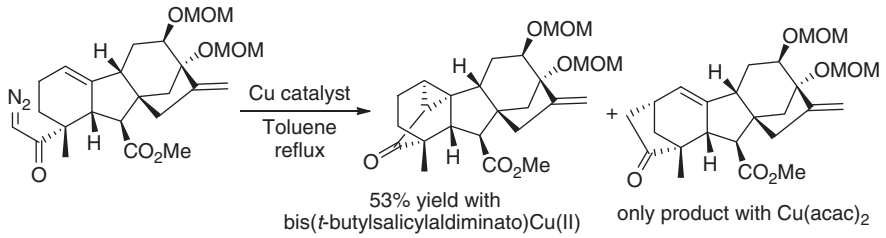
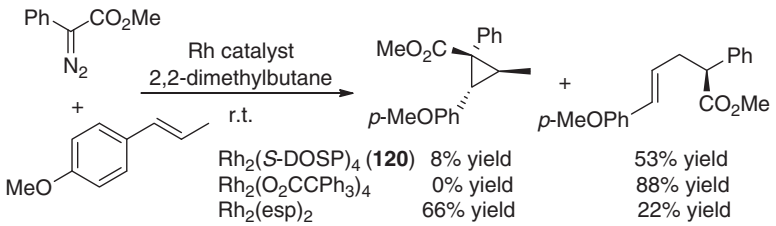


(16)

In the case of intermolecular reactions, Rh is more prone to promote C–H insertions than Cu[709] or Ag.[150] The chemoselectivity depends on the electronic and steric properties of the alkene, the donor/acceptor carbenoid, and the ligand of Rh catalysts.[149,710,711]

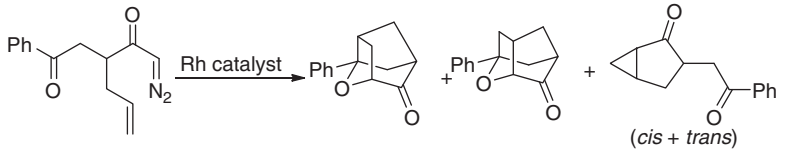


(17)

4.20.4.1.1.4 Other competing reactions

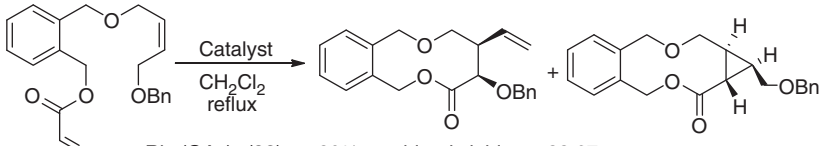
Depending on the nature of the metal and ligand, metal–carbenoids can undergo one-electron redox processes leading to formation of radicals. This is the mechanism proposed for some cyclopropanations and some competitive dimerizations, although it would be possible to envisage other synthetic uses such as cyclizations or polymerizations.[712]

The presence of unshared electron pairs in the substrate may produce the formation of ylides (sulfonium, oxonium, carbonyl, and nitrogen)[2] instead of the cyclopropanation reaction. The electrophilic character of the Rh catalyst seems to be responsible for the cyclopropanation/ylide formation chemoselectivity in the case of intramolecular reactions.[679] In fact, this reaction has been used for consecutive ylide formation and intramolecular 1,3-dipolar reaction using the formed ylide and the alkene.[713,714] In the case of macrolide formation by intramolecular cyclopropanation, a competitive oxonium ylide formation and [2,3]-sigmatropic rearrangement was detected, which was clearly favored in the case of Cu catalysts, whereas Rh catalysts were more selective to cyclopropanation.[499]



$Rh_2(OAc)_4$ (**36**)	10%	47%	37%
$Rh_2(tfa)_4$	34%	12%	30%
$Rh_2(cap)_4$	12%	52%	32%

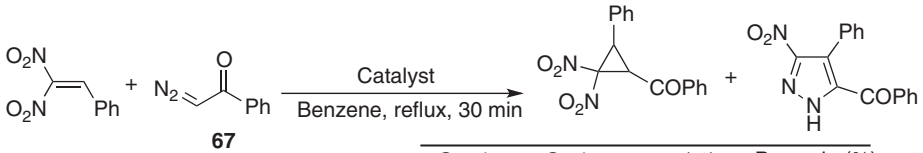
(18)



$Rh_2(OAc)_4$ (**36**)	80% combined yield	33:67
$Cu(MeCN)_4PF_6$	62% combined yield	74:26

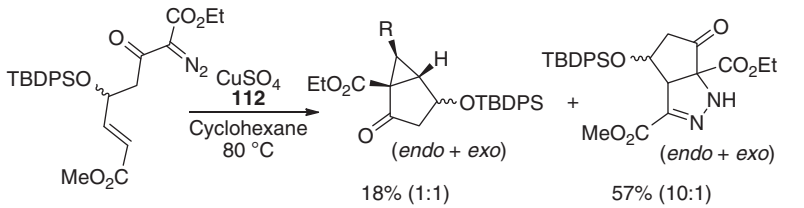
(19)

Diazo compounds are able to act as 1,3-dipoles in a noncatalyzed way. This route is competitive in some intermolecular[693] and intramolecular[715] cyclopropanations of electron-deficient alkenes.



Catalyst	Cyclopropane (%)	Pyrazole (%)
–	28	58
$Mo(CO)_6$	70	15

(20)



(21)

4.20.4.1.2 Diastereoselectivity (cis/trans-selectivity)

It is widely accepted that the *cis*/*trans*-selectivity in the cyclopropanation of simple alkenes with diazoacetates is mainly controlled by the steric interaction between the ester group of the metal-carbenoid and the substituent of the alkene, at least in those reactions taking place through a three-membered ring transition state, such as Cu-[84,716] and Ru[87,716,717]-catalyzed cyclopropanations. Under such conditions, a slight *trans*-preference is usually obtained according to the slightly higher stability of the transition state,[718] unless a highly bulky group, such as 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate,[338,417] is used in the ester moiety, for which a high *trans*-preference is found. Even in the case of simple alkyl diazoacetates and alkenes, the steric hindrance around the active site of the catalyst may have an important influence on the stereochemical course of the reaction. This is the case of the very high

trans-selectivity obtained in the cyclopropanation of styrene with ethyl diazoacetate **12** using Co–salen (98:2 with *tert*-butyl diazoacetate **133**),[719] Ru–pybox (93:7),[720] Ru–porphyrin in solution (96:4)[721] and supported on polystyrene (up to 93:7),[613] Cu-iminodiazaphospholidine (up to 98:2),[722] or Co-bis(2-pyridylimino)isoindole (up to 95:5).[640] High *trans*-preference has also been described with other bulky diazoesters, like succinimidyl diazoacetate **70** with a number of alkenes in the reactions catalyzed by an Ru catalyst (**134**).[145]

In contrast, some related catalysts have allowed obtaining *cis*-selectivity in the same reaction, from modest values with Cu–box (up to 65:35),[723] Rh_2-[ethyl 2-oxoazetidine-4(*S*)-carboxylate]$_4$ (73:27),[724] or $[(\eta^5\text{-}C_5H_5)(CO)_2Fe(THF)][BF_4]$ (85:15),[725] to very good results with Ru-salen (up to 96:4 with *tert*-butyl diazoacetate **133**)[726] and analogous PNNP ligands (up to 95:5),[632] Cu-trispyrazolylborate (up to 98:2),[371] Rh_2-[*ortho*-metalated arylphosphine]$_2(OOCCF_3)_2$ (up to 90:10),[727] or Rh-iminoNHC (up to >99:1).[548]

Both the improved *trans*-selectivity and the reversal to *cis*-selectivity have been explained by steric hindrance around the metal–carbenoid due to geometrical constraints imposed by the structure of the catalytic complex. In some cases those constraints have been simply proposed, for example, in the approach of styrene to the Rh_2-[*ortho*-metalated arylphosphine]$_2(OOCCF_3)_2$ complexes.[540] The presence of bulky groups in two of the possible quadrants should promote the formation of a major intermediate A_1, and it also should condition the approach of styrene to minimize the steric interaction of the phenyl group with those bulky groups of the complex in a transition state A_2. In other cases molecular modeling has been used to corroborate these kinds of hypothesis, for example, with Ru–PNNP complexes.[632] In such a case the tetradentate ligand prompts the carbenoid to an axial position, and the presence of the two phenylphosphino groups hinders the approach of styrene in a *trans*-fashion. DFT calculations with the monomeric Rh–iminoNHC complex[100] have shown that the most probable reaction pathway is in this case the formation of a metallacyclobutane, and the approach of styrene to coordinate Rh–carbenoid is the determining step for diastereoselectivity. The steric hindrance of the bulky aryl substituent of the imine moiety should be responsible for the high *cis*-selectivity obtained with this kind of complex (Figure 1).

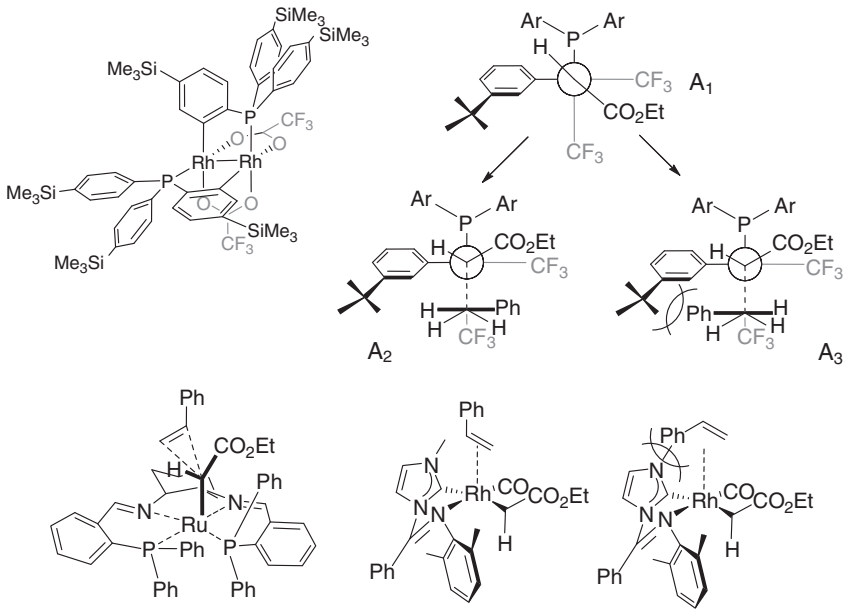
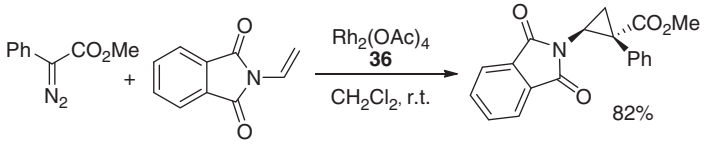


Figure 1 Stereochemical models explaining the *cis*-selectivity obtained with some rhodium–carbenoid complexes.

A similar effect may be produced by the presence of the support in the case of immobilized catalysts. Simple adsorption usually does not modify, or simply reduces the high selectivity observed in solution, as it happens with high *cis*-selective Cu[367] and Fe[728] catalysts. On the contrary, the electrostatic immobilization of copper catalysts on clays, and the forced proximity between the positive charged catalyst and the negatively charged surface induced by the use of solvents with low dielectric constant, produces strong effects on the diastereoselectivity, with significant *cis*-selectivity (69:31),[729] mainly in the case of using C_1-symmetric ligands (up to 91:9 *cis*/*trans*).[406,730]

The prediction is by far more difficult when both alkene and diazocompound bear more substituents of different nature.[731] Donor/acceptor carbenoids, derived from aryl- or vinyldiazoacetates, are also commonly used in cyclopropanation reactions. In general cyclopropanation of monosubstituted alkenes leads to very high diastereoselectivity toward the product with the aromatic group and the substituent of the alkene in *cis*-relative position, for example, with Rh catalysts,[212] but also moderate to high diastereoselectivity has been obtained in the thermal cyclopropanation with aryldiazoacetates.[51] This behavior has been also observed with Cu catalysts and styrene as substrate,[380] in the Rh-catalyzed cyclopropanation of *N*-vinylphthalimide with

aryldiazoacetates,[167] in the reaction of vinyldiazolactone with different alkenes catalyzed by Rh[215] or Ir[216] complexes, and even with the more reluctant α-alkyl diazoacetates and Rh catalysts.[526,732]



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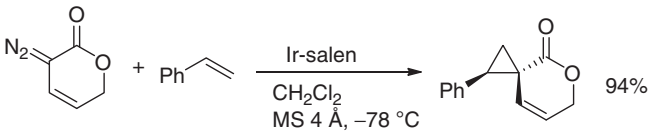

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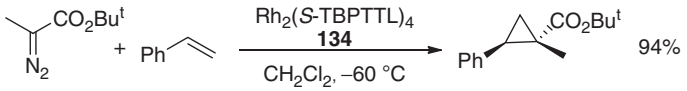
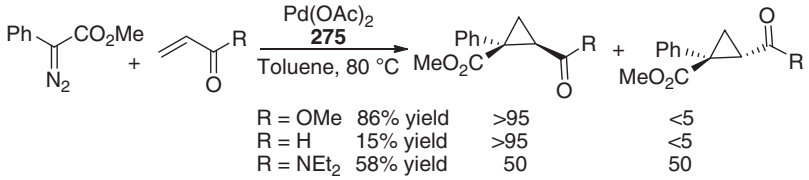


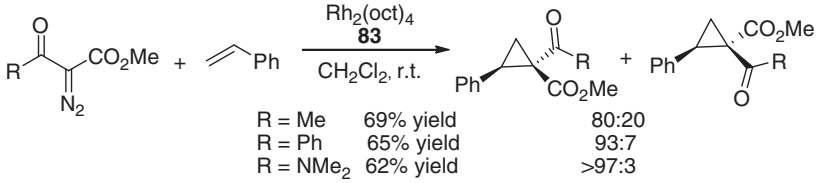
(24)

Cyclopropanation of electron-deficient alkenes with Pd catalysts[173] leads to the product with the carboxylate and the electron-withdrawing group in *cis*-relative position in the case of acrylates and acrolein (up to >95:5), whereas other substrates such as acrylonitrile or acrylamide do not produce any diastereoselectivity. In those cases a mechanism consisting of 1,3-dipolar cycloaddition of diazo compound and nitrogen extrusion has been proposed.



(25)

In the case of acceptor/acceptor diazo compounds, the nature of each acceptor group conditions its *trans*-directing ability, which increases in the order carboxylate < methyl ketone < aryl ketone < amide.[178] Thus, very high diastereoselectivity can be obtained with unsymmetrical malonate derivatives containing an ester and an amide group in the reaction with monosubstituted alkenes, leading to the cyclopropane with the ester and the alkene substituent in relative *cis*-position.



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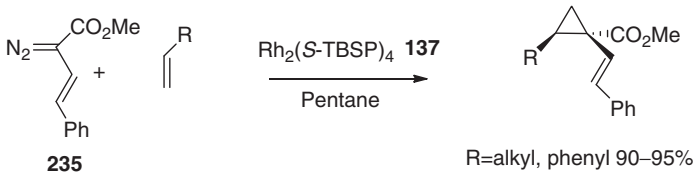
4.20.4.1.3 Solvent effects

The influence of different ligands or reactants in the stereoselectivity of the addition reactions of ketocarbenoids to alkenes has been profusely studied. Most times, the solvent acts as a passive spectator of the reaction. However, in some cases the choice of solvent has a dramatic effect not only on the rate of the reaction but also on the diastereo- and enantioselectivity. The focus here is on some examples of the solvent effects described up to date, in ketocarbenoids additions to alkenes and in the performance of these reactions in nonclassical solvents such as water, fluorous solvents, or ionic liquids.

The first solvent effect was described by Davies and coworkers, who used Rh carboxylate derivatives as catalysts in the cyclopropanation reactions of alkenes with vinyldiazoacetates. In this case, the use of pentane as the solvent provided a dramatic increase in enantiocontrol.[733,734]

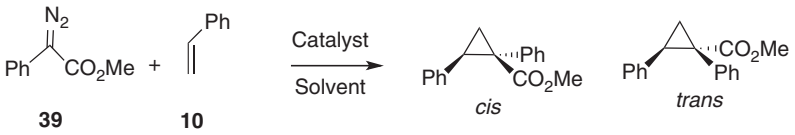


(27)

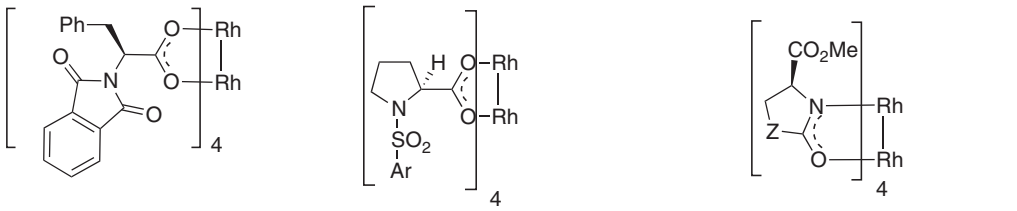
The same effect was described by Doyle and coworkers[735] in the reaction of methyl phenyldiazoacetate **39** with styrene **10** catalyzed by homochiral dirhodium(II) prolinates in pentane. However, the positive influence of pentane on enantiocontrol appears to be specific to some ligands such as prolinates as with carboxylates derived from phtaloimidates a reversal in % *ee* is observed, and there is no effect of pentane on enantiocontrol with a carboxamidate such as Rh_2(4*S*-TBOIM) **135**. Pentane appears to influence the alignment of prolinate ligands on dirhodium(II) complexes to increase enantiocontrol; the more rigid structural arrangement of chiral dirhodium(II) carboxamidates prevents a similar solvent effect (Table 5).

Table 5 Solvent effect on cyclopropanation reactions of methyl phenyldiazoacetate **39** with styrene **10**

Catalyst	*Solvent*	*Yield (%)*	trans/cis	ee *(*trans*) (%)*
136	CH_2Cl_2	95	98:2	34
136	Pentane	82	96:4	16
Rh_2(*S*-TBSP)$_4$ **137**	CH_2Cl_2	77	97:3	61
Rh_2(*S*-TBSP)$_4$ **137**	Pentane	73	96:4	85
Rh_2(4*S*-TBOIM)$_4$ **135**	CH_2Cl_2	63	95:5	77
Rh_2(4*S*-TBOIM)$_4$ **135**	Pentane	69	94:6	75

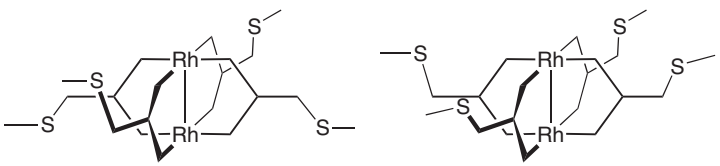


Catalyst:



(28)

Davies has proposed two possible explanations for these solvent effects on enantioselectivity. The first one invokes steric arguments, in which different rotamers of the chiral complex are differently stabilized depending on the solvent. The dirhodium tetracarboxylate complexes can adopt different orientations by free rotation about the proline carboxylate C–C bond and the N–S bond between the proline nitrogen and the sulfonyl group but just one of the rotamers can induce high enantioselectivities due to its high symmetry and more hindered catalytic sites. Other possible rotamers possess one rhodium site sterically unencumbered. The effect of the solvent applied to a major stabilization of rotamer **138** in pentane, whereas in CH_2Cl_2 a less selective rotamer is predominant. This theory agrees with Doyle's findings[735,736] in which no variability in % *ee* values was observed as a function of solvent when using chiral dirhodium(II) carboxamidates due to the rigidity of their structures.



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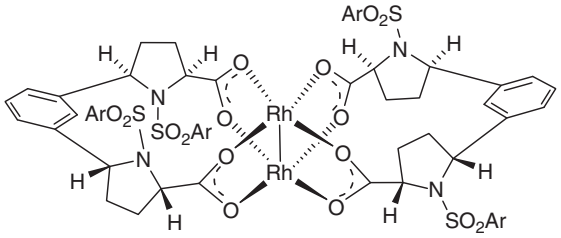
To test this theory, Davies synthesized rigid rhodium complexes bearing bridging prolinate ligands.[532] The presence of carboxylate ligands tethered to each other hinders the rotation.



Ar = *p*-Bu^{t}C$_6$H$_4$: Rh$_2$(*S*-biTBSP)$_4$ **139**

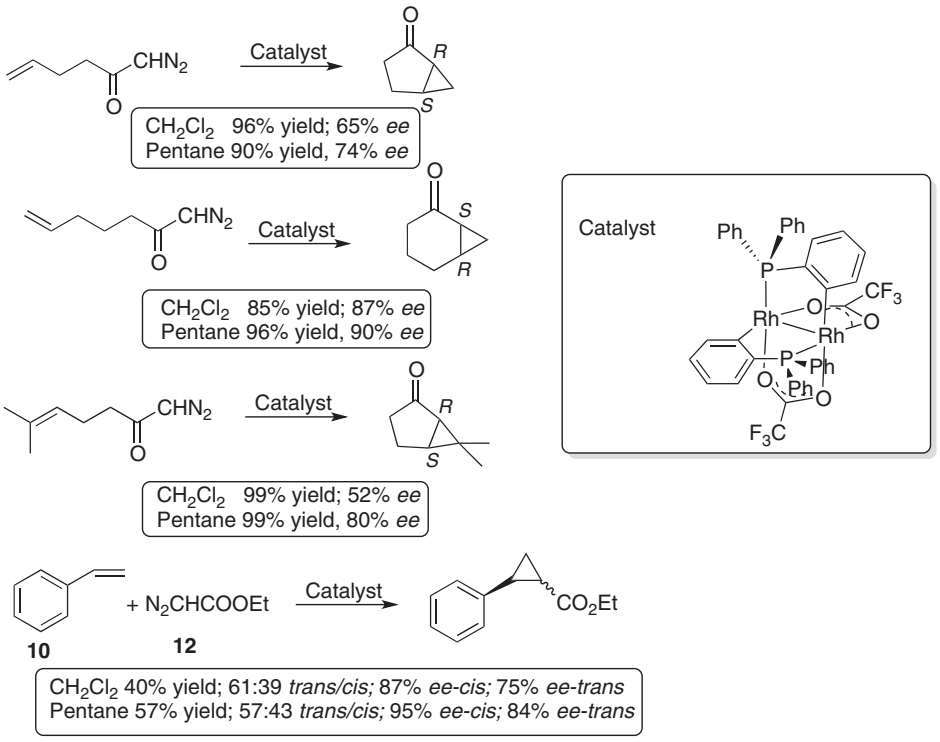
Ar = 2,3,4-triPr^{i}C$_6$H$_4$: Rh$_2$(*S*-biTISP)$_4$ **140**

In this case no dependence of the enantioselectivity was observed with Rh$_2$(*S*-biTBSP)$_4$ **139** catalyst, although a strong solvent effect was described for Rh$_2$(*S*-biTISP)$_4$ **140** (from 74% *ee* in pentane to 90% in CH_2Cl_2) this trend being opposite to the one described previously for rhodium prolinates. As the reason for this is not at all clear, it appears that the solvent effects are more complicated than just the rotation within the carboxylate ligands.

The other explanation that Davies has suggested involves electronic effects. The electronic nature of the substrate and the catalyst can affect the charge separation at the transition state in which the carbene attracts the more electron-rich carbon atom of the olefin while the other alkene carbon becomes more electropositive. Davies suggested that the solvent polarity could play a role in the timing of the transition state.

According to this explanation, solvents of high dielectric constant favor an early transition state in which the styrene molecule is farther away from the rhodium and therefore in a less chiral environment. In pentane, the charge separation is not stabilized at greater distances, the transition state must be later, and the olefin must be closer to the carbene and therefore in a more chiral environment.

The same effect has been observed when using chiral dirhodium complexes with *ortho*-metalated arylphosphine ligands in intra- and intermolecular cyclopropanation reactions (**Scheme 20**).[737] In this case, the best enantioselectivities were obtained using pentane at reflux temperature.

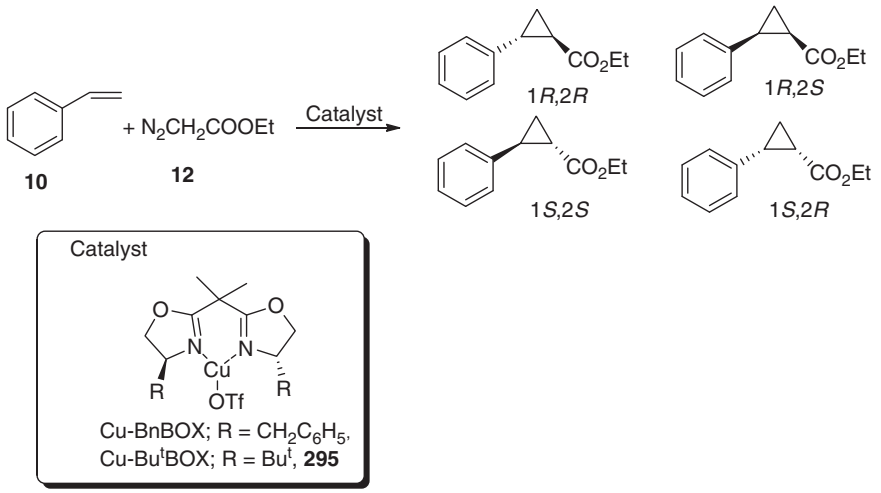


Scheme 20

Mayoral and coworkers[738] described the solvent effect in the reaction of styrene **10** with ethyl diazoacetate **12**, promoted by the complexes of two different bis-oxazolines with Cu(I) and Cu(II) salts – chloride and triflate – in CH_2Cl_2 and nitroethane. It was noticed that the use of nitroethane reduced the selectivity with regard to the diazoacetate, and also slightly reduced the *trans*/*cis*-selectivity. The influence of the solvent and the counterion on the enantioselectivity is explained on the basis of their influence in the disproportionation of Cu(I) to Cu(II) and Cu(0), the latter acting as a nonchiral catalyst species (**Table 6**).

Table 6 Solvent effects on the asymmetric cyclopropanation reaction between styrene **10** and ethyl diazoacetate **12** catalyzed by Cu–bisoxazoline complexes

Catalyst	*Solvent*	trans/cis	ee trans *(%)*	ee cis *(%)*
Cu-BnBOX	CH_2Cl_2	68:32	59	53
Cu-BnBOX	$EtNO_2$	64:36	55	45
Cu-^{t}BuBOX **293**	CH_2Cl_2	71:29	94	91
Cu-^{t}BuBOX **293**	$EtNO_2$	68:32	78	74



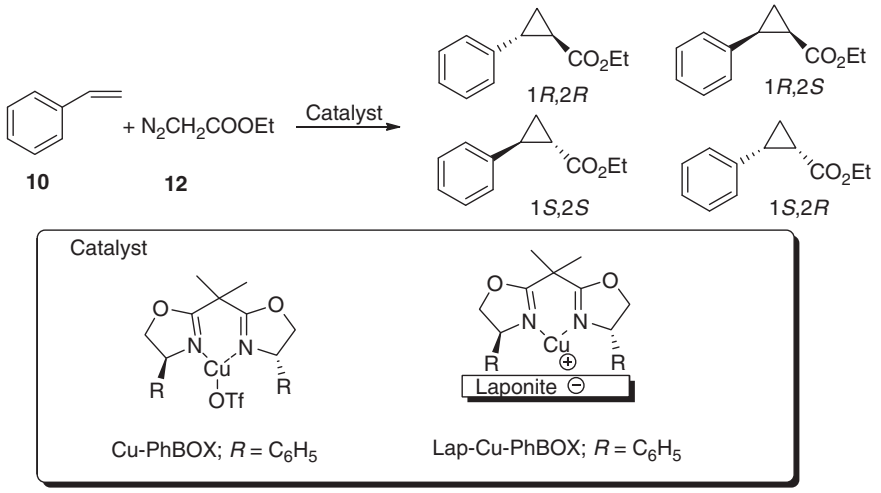
(29)

Dielectric properties of the reaction solvent have been also invoked by Mayoral and coworkers[739,740] as the matter for the surface effect observed on enhancement and reversal of enantioselectivities in cyclopropanation reactions catalyzed by Cu–bisoxazoline and Cu–pyridinoxazolines complexes immobilized onto laponite by ionic exchange.

In this case, the right choice of solvent can force the complex to approach the surface, including it in the steric environment of the active center responsible for the asymmetric induction (Table 7).

Table 7 Solvent effects on cyclopropanation reaction between styrene **10** and ethyl diazoacetate **12** catalyzed by bisoxazoline–Cu complexes immobilized onto laponite

Catalyst	*Solvent*	trans/cis	ee trans *(%)*	ee cis *(%)*
Cu-PhBOX (Cu-**217**)	CH_2Cl_2	71:29	54 (1*S*)	42 (1*S*)
Lap-Cu-PhBOX	CH_2Cl_2	61:39	49 (1*S*)	24 (1*S*)
Lap-Cu-PhBOX	Styrene	39:61	7 (1*S*)	34 (1*R*)
Lap-Cu-PhBOX	Toluene	40:60	3 (1*S*)	21 (1*R*)



(30)

Jessop and coworkers[741] carried out an elegant study of the influence of solvent on the enantioselectivity of cyclopropanations catalyzed by dirhodium carboxylate complexes. These results in both supercritical fluids and noncoordinating solvents confirm a strong dependence of the enantioselectivity on the dielectric constant of the medium. However, in coordinating solvents or solvent/additive mixtures, the dielectric constant is not the sole factor affecting selectivity. In fact, the enantioselectivity in such solutions is, in some manner, strongly dependent on the coordinating ability or nucleophilicity of the solvent or additive. Although coordinating solvents enhance the enantioselectivity relative to what one would expect on the basis of the dielectric constant, the best enantioselectivity was obtained in solvents or in the presence of reagents that showed no UV/Vis evidence of binding to the catalyst. Three different explanations are offered for the effect of coordinating solvents or reagents; coordination of the solvent to form an $LRh(RCO_2)_4Rh{=}CPhCO_2Me$ complex, disruption of the $Rh_2(RCO_2)_4$ core to create dangling carboxylates, or coordination of L to the carbene to form an ylide. There is as yet insufficient evidence to distinguish between these; it is possible that all three occur with different coordinating species (Figure 2).

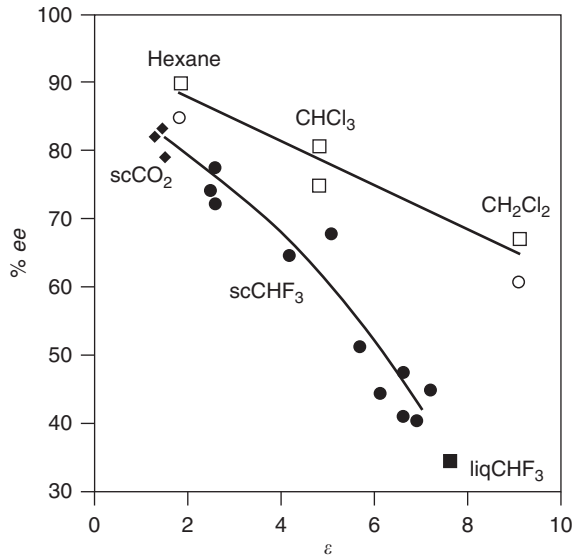
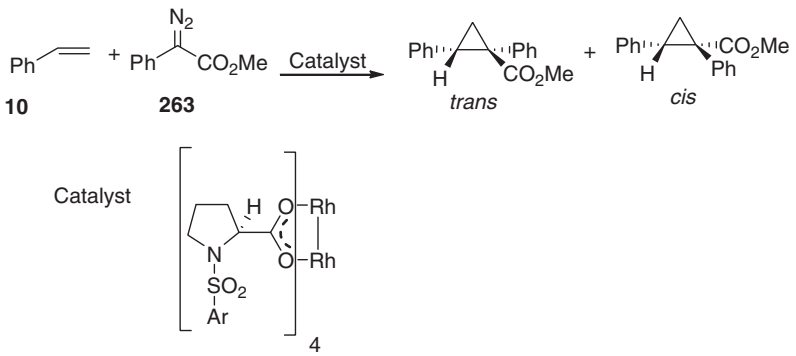


Figure 2 The dependence of the enantiomeric excess of **2** on the dielectric constant of $scCHF_3$ (●), $scCO_2$ (◆), liquid CHF_3 (■), or noncoordinating liquid solvents (literature[4] date ○, our data □). The two data points for $CHCl_3$ correspond to the amylene- (lower point) and ethanol-stabilized (upper point) solvents. Reprinted with permission from Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7638–7647.

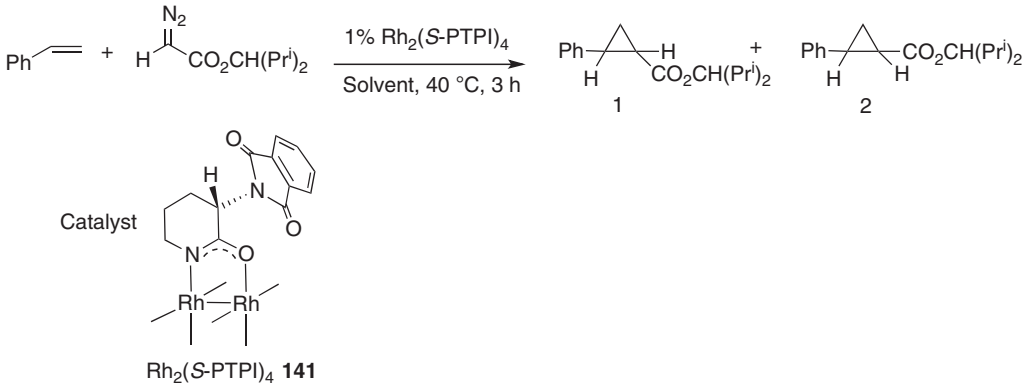


(31)

Solvents effects have also been described when using $Rh_2(S\text{-PTPI})_4$[134] **141** as a catalyst. In this case, the use of ethereal solvents such as ether or THF has a positive effect in enantioselectivities of cyclopropanation reactions of styrene **10** with several diazoacetates, whereas diastereoselectivity remains unaffected. The effect of the solvent is not well understood, but the researchers observed a major improvement by switching from CH_2Cl_2 to ether with diazoacetates bearing bulkier moieties in the ester group such as ethyl, Bu^t, or dicyclohexylmethyl (Table 8).

Table 8 Solvent effects on enantioselectivities in cyclopropanation reaction between styrene **10** and 2,3,4-trimethyl-3-penthyl diazoacetate **142** catalyzed by $Rh_2(S\text{-PTPI})_4$[137] **141**

Solvent	ee trans *(%)*	ee cis *(%)*
CH_2Cl_2	49	63
Benzene	79	76
Et_2O	98	96
THF	79	82



$Rh_2(S\text{-PTPI})_4$ **141**

(32)

The presence of water has been sometimes reported as detrimental to obtaining good enantioselectivies. Jessop and coworkers[741] tested the effect of controlled amounts of water on the enantioselectivity when using methanol as reaction solvent and found that the enantiomeric excess dropped drastically. This effect has also been described by other researchers, thus it is not surprising that only few examples appeared in the literature related to the study of cyclopropanation reactions in water, and even less under chiral conditions.

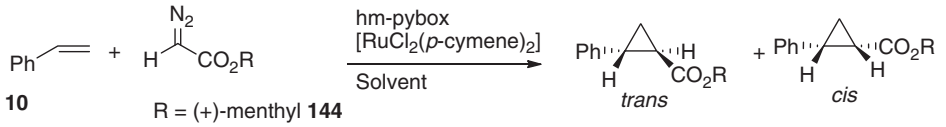
The use of water as solvent responds to the recent environmental demands for organic synthesis and catalysis, in substituting classical and hazardous solvents such as halogenated compounds by nonhalogenated solvents or aqueous and protic media.

The performance of carbene transfer in water can be tackled either by using a water-soluble chiral complex or by working under micellar conditions.

The first possibility was explored by Nishiyama and coworkers[594] by developing soluble pybox ligands, bearing hydroxyl groups and the use of their Ru-complexes as catalysts for cyclopropanation reactions of terminal alkenes with diazo esters using water or alcohol–water mixtures as solvent. In this case, the use of water as additive induces a dramatic increase in enantioselectivities from 8% to 78% *ee* (Table 9).

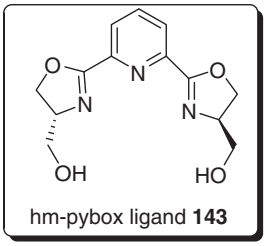
Table 9 Effect of water as additive in the enantioselectivities of cyclopropanation reaction between (1*S*,2*R*,5*S*)-menthyl diazoacetate **144** and styrene **10** catalyzed by hm-pybox(**143**)–Cu complex

Solvent	ee trans *(%)*	ee cis *(%)*
THF	8	30
Toluene	8	28
$THF+H_2O$	78	45
$Toluene+H_2O$	88	51



10

R = (+)-menthyl **144**



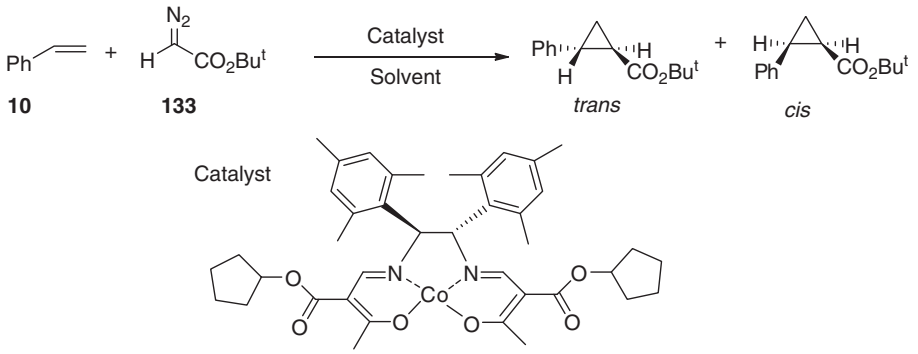
hm-pybox ligand **143**

(33)

In the same year, Yamada and coworkers[654] reported high enantioselectivities in the cyclopropanation reactions in alcoholic and aqueous solvents catalyzed by optically active α-ketoiminato cobalt(II) complex. In this case, positive effects were observed both in the rate of the reaction and enantioselectivity when using alcohols as solvents. The researchers suggested a strong coordination of the alcohol to the cobalt atom to explain the positive effects. In contrast to the previous work of Nishiyama, the cobalt complex was not soluble in water (Table 10).

Table 10 Water effect on the results of cyclopropanation reaction between styrene **10** and *tert*-butyldiazoacetate **133**

Solvent	*Yield*	trans/cis	ee trans *(%)*
$CHCl_3$	40	70:30	76
Toluene	31	72:28	76
THF	74	77:23	87
THF+H_2O	58	78:22	88
MeOH	88	83:17	93
MeOH+H_2O	89	83:17	92



(34)

In an attempt to rationalize these results, Wurz and Charette[489] carried out a study of diazo-mediated cyclopropanation reactions in water using hydrophobic catalysts and nonwater-soluble alkenes.

Their idea was to create a micellar system in which the catalyst and the alkene would remain closer while the soluble diazo compound would diffuse from the aqueous phase to the organic phase, where the reaction takes place.

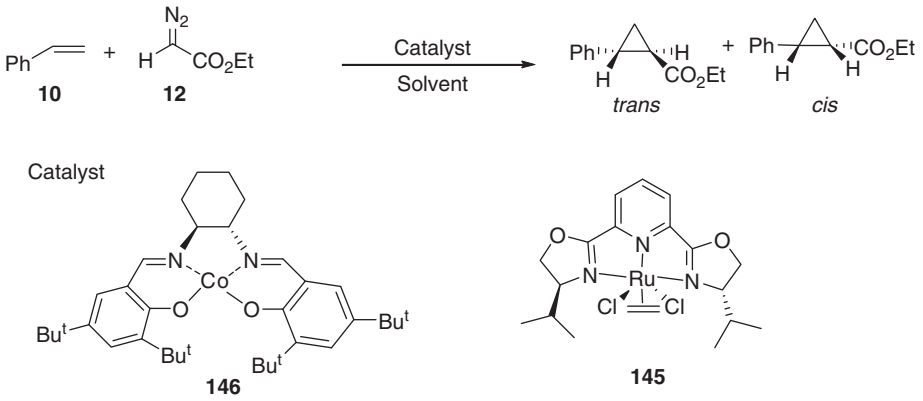
A number of nonchiral rhodium carboxylate catalysts were screened for cyclopropanation reactions with several alkenes in water. Results were compared with those obtained in dry CH_2Cl_2.

It was concluded that low yields were obtained with water-soluble catalysts, whereas high yields were obtained with hydrophobic catalysts. This procedure also allowed the *in situ* generation of the diazo compound from sodium nitrite and amino derivatives in water.

Asymmetric cyclopropanation reactions were also studied. Pr^iPybox–Ru(II)–ethylene **145** and Co–salen **146** complexes were used as chiral catalyst in the cyclopropanation reaction of styrene **10** with ethyl diazoacetate **12**. The results revealed the obtaining of high diastereo and enantioselectivities close to the ones obtained in CH_2Cl_2. In the case of **146**, an increase in reactions rates was also observed (Table 11).

Table 11 Solvent effect in cyclopropanation reactions between styrene **10** and ethyldiazoacetate **12** catalyzed by Co–salen and Ru–pybox complexes

Catalyst	*Solvent*	*Yield*	trans/cis	ee trans *(%)*
146	THF	20	–	–
146	H_2O	61	66:34	22
145	CH_2Cl_2	20	96:4	86
145	H_2O	58	95:5	90



(35)

Results of Wurz and Charette revealed that water is a suitable solvent to use for the cyclopropanation of alkenes with α-diazoester reagents.

More recently, dirhodium(II) *ortho*-metalated aryl phosphine complexes have also been tested as catalysts in the cyclopropanation reaction of styrene **10** and ethyl diazoacetate **12** in water. The work of Úbeda and coworkers[540] showed an increase in the reaction rate in water compared with the reactions carried out in pentane, while diastereoselectivities dropped from 90:10 to 71:29 and enantioselectivities were not affected. In the case of using water as reaction solvent, competitive reactions such as dimerization of the ethyl diazoacetate **12** and O–H insertion reaction were also promoted.

This catalytic reaction has also been studied under micellar conditions by adding a surfactant to the aqueous medium. The anionic surfactant sodium dodecyl sulfate (SDS) and the cationic cetyltrimethylammonium hydrogensulfate were tested. Not only diastereoselectivities but also the percentage of side products coming from dimerization of ethyl diazoacetate **12** were slightly improved by the use of surfactants.

The use of neoteric solvents in carbene addition to unsaturated compounds does not only respond to the need of substituting hazardous and contaminant solvents but also to the need of recovering the homogeneous catalyst. In this way, ionic liquids and fluorous solvents have attracted great attention. The advantage of using these new solvents lies in the reusability of the catalyst after extraction of the products from the reaction medium.

Starting with ionic liquids (ILs), one can find in the literature several examples of the use of these compounds as solvents both in nonchiral and chiral catalysis of the addition reaction of ketocarbenoids to alkenes. Thus $Rh_2(OAc)_4$ **36**, immobilized in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid, [bmim]PF_6, was used in alkenes cyclopropanation with ethyl diazoacetate **12**.[742] Cyclopropanecarboxylates were obtained in excellent yields with high *trans*-selectivity. The recovery of the catalyst is facilitated by the hydrophobic nature of [bmim][PF_6]. The recovered ionic liquid containing $Rh_2(OAc)_4$ **36** can be reused up to five times with only a gradual decrease in activity.

In the same way, the complex {[HC(3,5-$Me_2Pz)_3$]Cu(NCMe)}BF_4 **147** catalyzed the transfer of the: $CHCO_2Et$ unit from ethyl diazoacetate **12** to alkenes and alkynes with very high yields and under biphasic conditions using [bmim][PF_6] and hexane as the reaction medium (**Figure 3**). The catalyst was recovered and reused for several cycles without any loss of activity (**Figure 3**).[369]

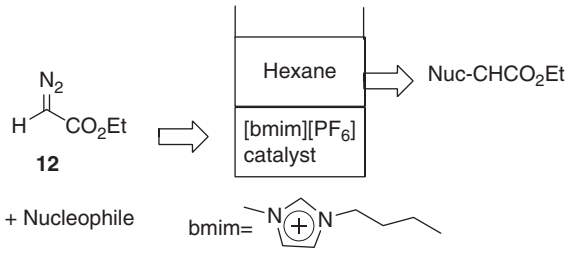
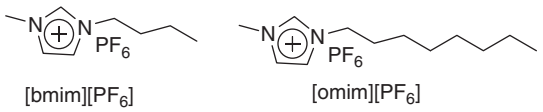


Figure 3 Biphasic cyclopropanation catalysis. The catalytic copper complex remains bounded to the ionic liquid phase, allowing easy recovery and reuse.

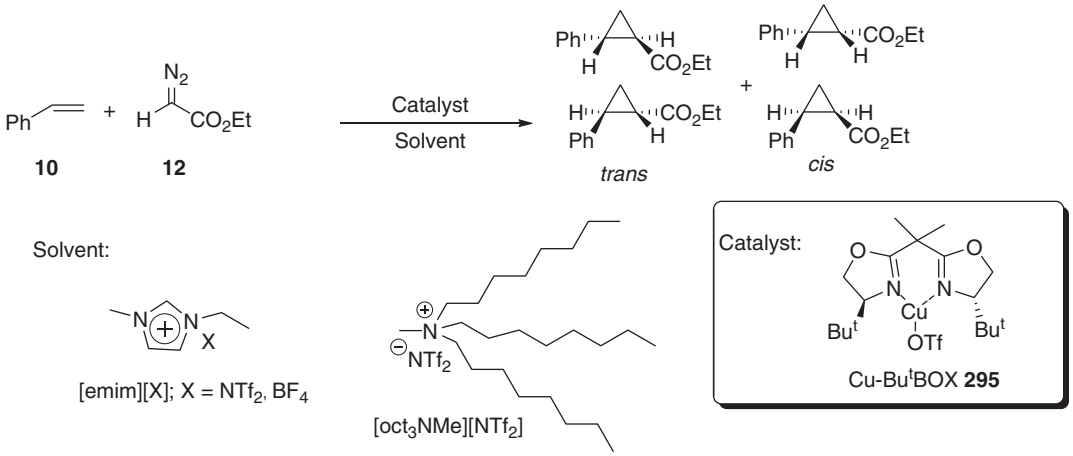
A nice example of the stabilization of the catalyst in ionic liquids was reported by Corma and coworkers[686] in the cyclopropanation reaction of alkenes with ethyl diazoacetate **12** catalyzed by $NaAuCl_4$ **148** and $KAu(CN)_2$ **149**. Gold catalysts being active and selective in cyclopropanation presented serious drawbacks associated with catalyst recovery and recycling, most of time due to deactivation of the catalyst by forming inactive large particles of Au(0) species.

In this study, ionic gold complexes in different imidazolium ILs ([bmim][PF_6] and [omim][PF_6]) were used as recoverable and reusable homogeneous catalysts in the cyclopropanation reaction of alkenes with ethyl diazoacetate **12** to give *cis*- and *trans*-cyclopropanes.



It was observed that the stability and performance of these gold salts is much higher in ILs than in typical solvents used in this reaction (e.g., 1,2-dichloroethane, CH_2Cl_2, and acetonitrile). Nonetheless, salt decomposition also occurred in the IL [bmim][PF_6], and gold nanoparticles were formed that could be stabilized by the IL, avoiding rapid agglomeration, in contrast to what occurs in conventional solvents, in which large gold metal agglomerates are formed in the first run.

The first study of asymmetric cyclopropanation reactions in ionic liquids was reported by Mayoral and coworkers.[743] Cyclopropanation of styrene **10** with ethyl diazoacetate **12** using chiral Cu–bisoxazolines complexes was carried out. A fine-tuning of both the coordinating ability of the cation and the polarity of the solvent allowed the optimization of the system. When using [emim][NTf_2] as a reaction medium, the catalytic system could be reused up to three times with any loss neither in activity nor in selectivities.



(36)

The same group[744] reported the importance of the stability of the complex in order to improve the recoverability of the catalytic system. Thus the use of azabis(oxazoline)–Cu complexes, more stable than their analogs based on bis(oxazoline) ligands, leads to improved recoverability (up to eight times) when these systems are used in an ionic liquid medium. The solution containing the chiral catalyst could even be reused in different enantioselective cyclopropanation reactions and still lead to high *ee* (>90%) (Figure 4).

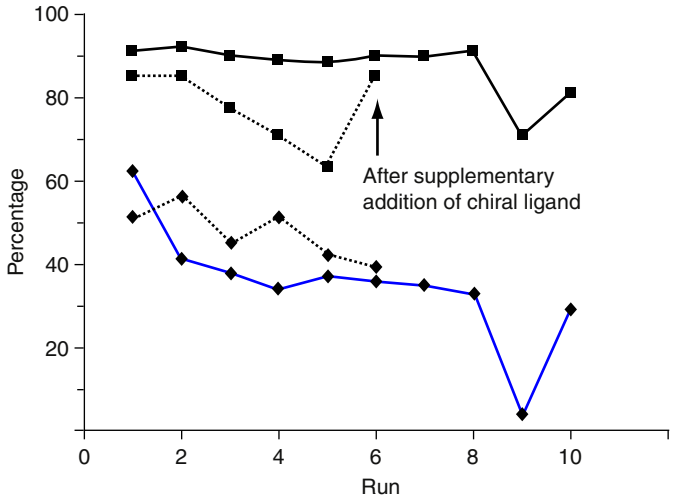
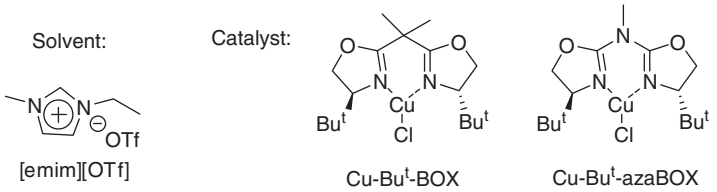


Figure 4 Resume of the solutions of azabis(oxazoline)–CuCl (**1**-CuCl(——)) and bis(oxazoline)–CuCl (**2**-CuCl (·····)) in [emim][OTf]: (■) %cc for *trans* isomers; (◆) %yield. Reprinted with permission from Fraile, J. M.; Garcia, J. I.; Herrerias, C. I.; *et al. Tetrahedron Lett.* **2004**, *45*, 6765–6768.

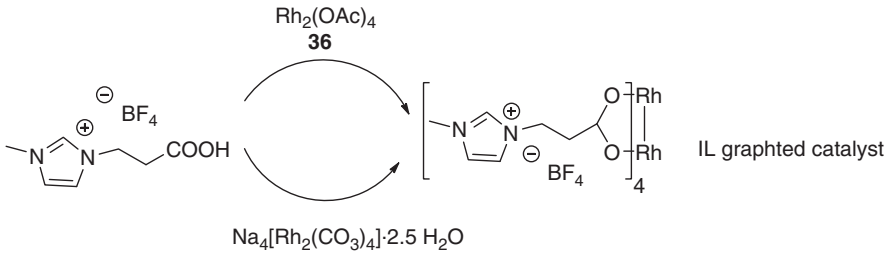


As ILs and anionic solids, such as laponite, can be used to obtain recoverable catalysts for reactions promoted by cationic chiral complexes it may be interesting to consider which one is preferred. In this sense, after a detailed study of Cu(II)–bisoxazoline complexes as cyclopropanation catalysts both in ionic liquids and immobilized onto laponite, Mayoral and coworkers[745] concluded that when the complex is very stable, catalyst recovery is efficient in both cases but solid catalysts have the advantage of easier handling.

When the complex is not so stable, the equilibrium between the complexed and free form of the metal may lead to the presence of nonchiral sites, with the consequent reduction in enantioselectivity. In this case the use of IL is advantageous because it avoids steric interactions between the chiral ligand and the support, which may shift the equilibrium toward the noncomplexed form.

Davies and coworkers[746] also reported the use of IL in asymmetric cyclopropanation reactions catalyzed by copper bisoxazoline complexes. In the reaction of styrene **10** and ethyl diazoacetate **12** good yields (85–90%) and excellent enantioselectivities (up to 98% *ee*) were reported, the catalyst being reusable up to four times. In this case, it was noticed that the purity of the IL has a great influence on the activity of the catalytic system.

An interesting approach to the use of IL is the one proponed by Forbes and coworkers[747] based on the design of task-specific ionic liquids (TSILs, **Scheme 21**). These IL further enhances the versatility of classical ionic liquids acting both as reagent and medium. In this work a tethered imidazolium carboxylate ligand was synthesized and a complex with Rh formed, getting for the first time a grafted IL–Rh complex applied in an IL medium. Although the yields in cyclopropanation reactions were moderate, this work opened the door to the design of ionic liquid grafted chiral ligands to be applied in metal–carbene chemistry.



Scheme 21

Finally, supported IL (SILF) have also been tested as reaction media in cyclopropanations catalyzed by bis(oxazoline)–copper complexes.[748]

Supporting thin layers of IL onto different solids presents the advantage of an easier recoverability of the catalyst. In this work also an effect of the nature of the support was observed, thus when using clay, the system behaves as a nearly two-dimensional nanoreactor in which the restrictions in rotational mobility and the proximity to the surface support produce variations in the stereo- and enantioselectivities, leading to a complete reversal of the overall selectivity of the reaction. This variation strongly depended on both the thickness of the film and the nature of the support. Only layered solids with negative charges in the layers (clays) give rise to this type of behavior, showing that the formation of ion pairs may be a decisive factor. This unexpected effect also shows the existence of differences between bulk and supported ionic liquid (**Figure 5**; **Table 12**).

The use of fluorinated solvents in ketocarbenoids addition reactions has been usually envisaged to the recovery of the catalyst. In most cases, catalysts should be modified in order to increase their solubility in the fluorous media.

Several catalytic systems have been described: nonchiral Rh carboxylates,[493,494] chiral dirhodium(II) complexes,[749] chiral fluorous bisoxazolines copper complexes,[750] and cobalt and copper complexes of perfluoroalkyl-substituted, C_2-symmetric *N* and *N,O* ligands.[639]

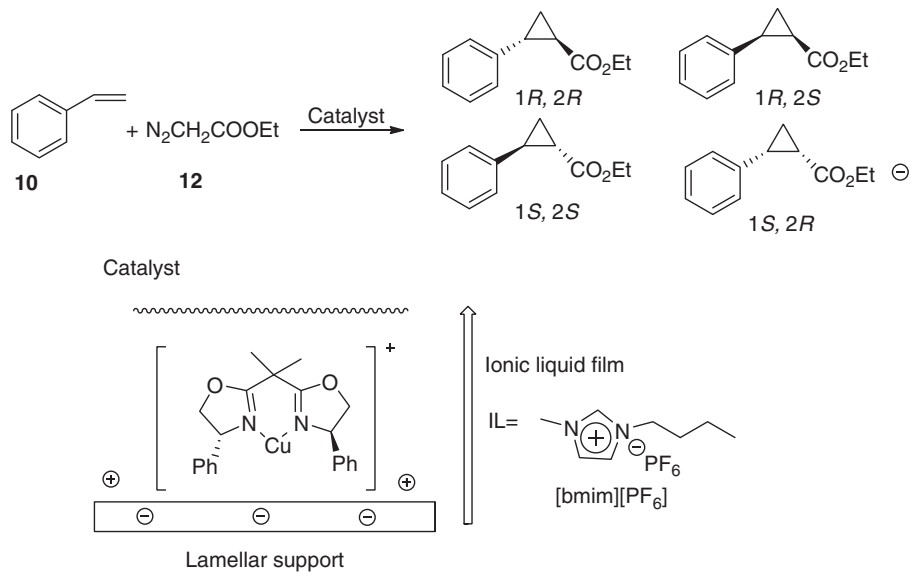
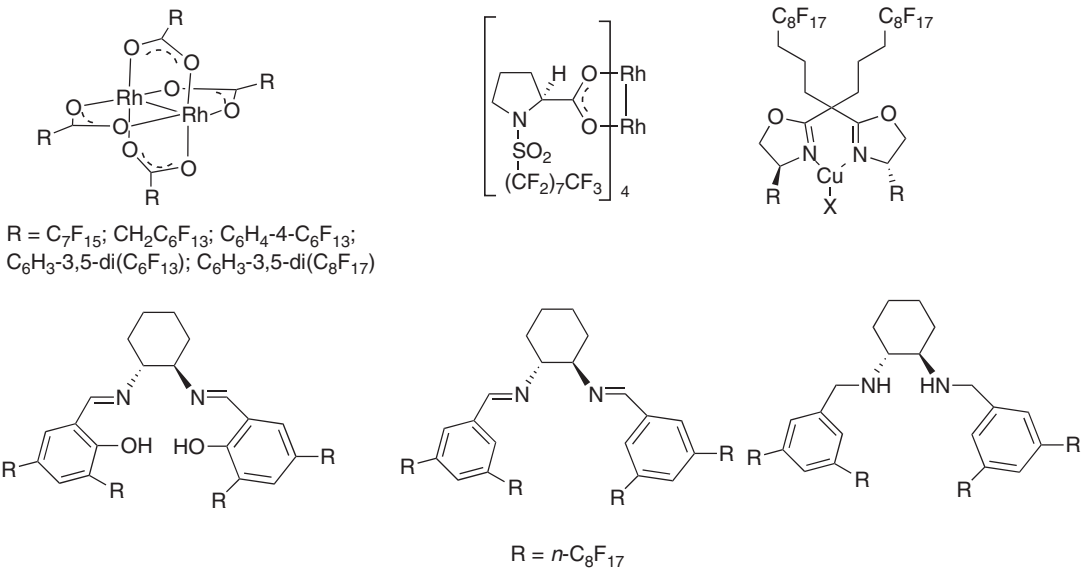


Figure 5 Heterogeneization of a chiral bis(oxazoline)–copper complex in a thin ionic liquid film onto a layered solid.

Table 12 Influence of the support on the selectivities of cyclopropanation reaction between styrene **10** and ethyl diazoacetate **12** catalyzed by solid-supported bisoxazoline–Cu complex/ionic liquids (IL)

Support	*IL/support*	trans/cis	ee trans *(%)*[a]	ee cis *(%)*[b]
Bentonite	0.05	57:43	47	4
Bentonite	0.01	22:78	6	–62
Graphite	0.05	68:32	54	45
Graphite	0.01	67:33	56	48
K10	0.03	36:64	27	–42
K10	0.01	23:77	5	–61

[a]Major enantiomer is 1*S*.
[b]Major enantiomer is 1*S* except with a minus sign that indicates that 1*R* is the major enantiomer.



Sometimes, no ligand modification is required in order to recover the catalyst in a fluorous media. Thus, Pérez and co-workers[751] described the use as catalyst of the complex $Tp^{Br3}Cu(NCMe)$ **150**, containing no fluorine atoms, in a perfluoropolyether Fomblin1 as solvent for the cyclopropanation of styrene **10** with ethyl diazoacetate **12**. The activities and

diastereoselectivities were identical to those observed under homogeneous conditions with the advantage of being able to use a fluorous separation technique for catalyst recycling (Figure 6; Table 13).

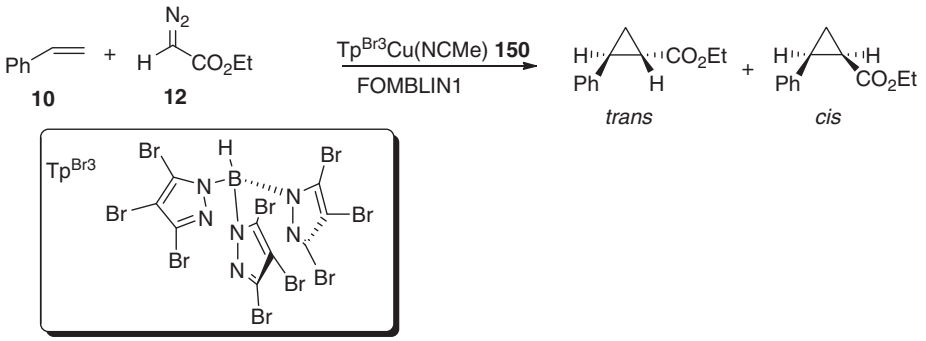


Figure 6 Cyclopropanation reaction in a fluorous medium using a tris(pyrazolyl)borate–copper catalyst.

Table 13 Results in cyclopropanation reaction of styrene **10** with ethyl diazoacetate **12** catalyzed by $Tp^{Br3}Cu$(NCMe) **150** in FOMBLIN1

Cycle	*Yield (%)*	trans/cis
1	90	60:40
2	90	59:41
3	85	60:40
4	93	58:42
5	91	57:43

Finally, the possibility of carrying out the reaction in the absence of any solvent has also been explored. These studies demonstrate that reactions involving donor/acceptor-substituted rhodium carbenoids can be conducted with very high turn over numbers (TONs) in the absence of solvent. When very active trapping agents are used, such as styrene and cyclopentadiene, the catalyst to substrate ratio can be as low as 0.6 ppm, resulting in TONs of up to 1.8 million. Donor/acceptor carbenoids are ideal for reactions with low catalyst loadings due to its better stabilization. They are still very reactive, but less prone to catalyst destruction and carbene dimerization. The solvent-free conditions greatly enhance the efficiency of the catalysts, presumably by favoring the productive bimolecular process for product formation over the unimolecular process for metal-carbenoid destruction.[520]

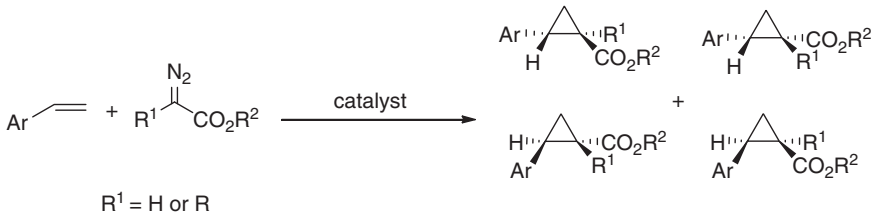
4.20.4.1.4 Nonasymmetric reactions

A huge number of alkenes have been studied for intermolecular cyclopropanation reactions by using ketocarbenoids during the period 1989–2012. However, some selected representative reactions will only be discussed in Sections 4.20.4.1.4.1–4.20.4.1.4.10 for the sake of conciseness. Works dealing with intermolecular asymmetric cyclopropanation reactions have experienced an exponential growth in the last years, above all from the point of view of asymmetric catalysis. Therefore, for the sake of readability and to avoid duplicating information, only nonenantioselective reactions will be discussed in the following sections, devoted to different kinds of alkenes, and asymmetric versions of these reactions will be next discussed in Sections 4.20.4.1.5.1 and 4.20.4.1.5.2.

Among all the intermolecular cyclopropanation reactions, those using styrenes as alkenes have a special relevancy, because every new catalyst described has been first tested with these particular substrates. As a consequence, the reactions with these kinds of alkenes will be described first.

4.20.4.1.4.1 The Benchmark reactions: Styrene derivatives+diazoacetic esters

The reactions of styrene **10** and styrene derivatives with diazoacetates have been used as the benchmark process to test the performance of many cyclopropanation catalysts. The cyclopropanation competes with the carbene dimerization to produce maleate and fumarate; for this reason slow addition of the diazo compound and an excess of alkene are used to reduce the dimerization and to increase the chemoselectivity of the reaction. The cyclopropanation leads to a mixture of *cis*- and *trans*-cyclopropanes so that control of diastereoselectivity is also important. Finally it is possible to use chiral catalysts leading to good enantioselectivities in *trans*- and *cis*-products (see Section 4.20.4.1.5.2).



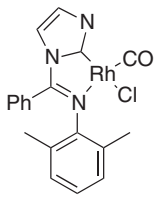
(37)

The following tables gather the most relevant results obtained with nonchiral homogeneous catalysts using alkyl diazoacetates or substituted diazoacetates (Table 14).

Table 14 Nonenantioselective cyclopropanations of styrene **10** with alkyl diazoacetates (R^1 = H)

Catalysts	*R^2*	*Alkene/diazoester*	*Yield (%)*	trans/cis	*References*
151	Et	5/1	98	1:99	548,752
151	Bu^t	5/11	99	1:99	548,752
152	Et	5/1	92	91:9	97
152	Bu^t	5/1	91	98:2	97
153	Et	5/1	93	83:17	97
154	Et	10/0.15	41	71:29	380
155	Et	5/1	98	2:98	371
Cu-**156**	Et	17/1	86	89:11	680
Ru-**157**	Et	–	100	93:7	567
Os-**158**	Et	1/1	76	91:9	567
Fe-**159**	Et	20/1	97	88:12	658
Ru-**160**[a]	Et	1/1–2	90	91:9	608
Ru-**161**	Et	1.5/1	91	76:24	605

[a]Reaction in water, catalyst recycled five times with closely similar results.



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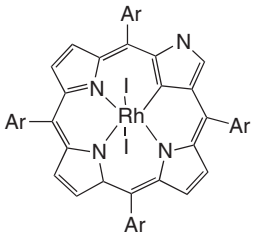
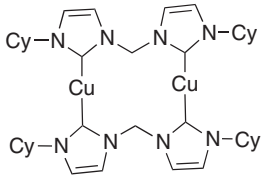


152 R = Ph
153 R = mesityl



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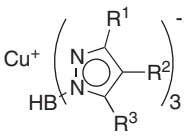
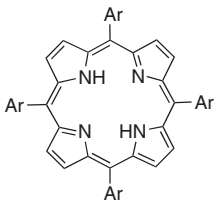


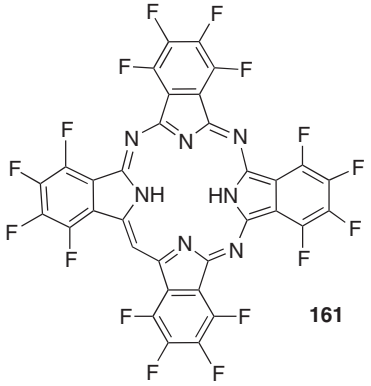
155

$CH_3C(CH_2N{=}PCp_3)_3$

156



157 TPP: Ar = C_6H_5
158 TTP: Ar = *p*-tolyl
159 TpFPP: Ar = C_6F_5
160 4-Glu TPP: Ar = Ph-O-Glu



161

Some of these catalysts have been also used in the cyclopropanation of *p*-substituted styrenes with diazoacetates and substituted diazoacetates (Tables 15–17).

Table 15 Nonenantioselective cyclopropanations of styrene **10** with substituted alkyl diazoacetates

Catalyst	*R^1*	*R^2*	*Alkene/DA*	*Yield (%)*	trans/cis	*References*
$Rh_2(TPA)_4$ **162**	Et	Et	3/1	92	95:5	495
$Rh_2(TPA)_4$ **162**	Me	Et	3/1	94	95:5	495
Ru-**161**	Bu	Et	3/1	99	95:5	495
154	Ph	Me	10/0.15	45	95:5	380
$AgSbF_6$	Ph	Me	–	96	97:3	150
$AgSbF_6$	PhCH=CH	Me	5–10/1	82	99:1	150
–	Ar	Me	5/1	57–97	56:44–95:5	51
154	Ph	Me	10/10.15	45	95:5	380
$Rh_2(OPiv)_4$ **86**	NO_2	Me	5/1	90	90:10	492

Abbreviation: DA, diazoacetate.

Table 16 Nonenantioselective reactions of styrenes with ethyl diazoacetate **12** (R^1=H; R^2=Et)

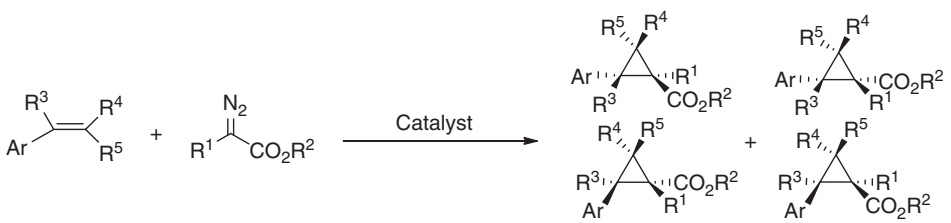
Catalyst	*Ar*	*Alkene/EDA*	*Yield (%)*	trans/cis	*References*
151	*p*-MeO-C_6H_4	5/1	99	<1:99	548,752
151	*p*-Cl-C_6H_4	5/1	99	<1:99	548,752
151	1-Naphthyl	5/1	94	<1:99	548,752
Fe-**159**	*p*-Me-C_6H_4	5/1	85	82:18	658
Fe-**159**	*p*-Cl-C_6H_4	5/1	86	86:14	658
Ru-10	*p*-Me-C_6H_4	1/1.2	94	91:9	608
Ru-10	*p*-MeO-C_6H_4	1/1.2	92	92:8	608
Ru-10	*p*-Cl-C_6H_4	1/1.2	90	89:1	608
Ru-10	*p*-Pr-C_6H_4	1/1.2	88	88:12	608
Ru-**161**	*p*-Me-C_6H_4	1–5/1	88	83:17	605
Ru-**161**	*p*-X-C_6H_4	1–5/1	88–81	86:14–82:18	605
Ru-**161**	*p*-CF_3-C_6H_4	1–5/1	81	80:20	605
Ru-**161**	*p*-NO_2-C_6H_4	1–5/1	83	83:17	605

Abbreviation: EDA, ethyl diazoacetate.

Table 17 Nonenantioselective cyclopropanations of styrenes with substituted alkyl diazoacetates

Catalyst	*Ar*	*R_1*	*R_2*	*Alkene/diazoester*	*Yield (%)*	trans/cis	*References*
$Rh_2(OPiv)_4$ **86**	*p*-MeO-C_6H_4	NO_2	Me	5:1	91	–	492
$Rh_2(OPiv)_4$ **86**	*p*-Me-C_6H_4	NO_2	Me	5:1	87	91:9	492
$Rh_2(TPA)_4$ **162**	*p*-F-C_6H_4	Et	Et	3:1	83	95:5	495
$Rh_2(TPA)_4$ **162**	*p*-$MeOC_6H_4$	Et	Et	3:1	91	95:5	495
$Rh_2(TPA)_4$ **162**	1-Naphthyl	Et	Et	3:1	80	95:5	495
$Rh_2(TPA)_4$ **162**	*p*-F-C_6H_4	Me	Et	3:1	97	95:5	495
$Rh_2(TPA)_4$ **162**	*p*-Me-C_6H_4	Me	Et	3:1	95	95:5	495
$Rh_2(TPA)_4$ **162**	1-Naphthyl	Me	Et	3:1	79	95:5	495
$Rh_2(TPA)_4$ **162**	2,3,5-C_6H_4	Me	Et	3:1	100	95:5	495
$Rh_2(TPA)_4$ **162**	*p*-F-C_6H_4	Bu	Et	3:1	96	95:5	495

In the same way, reactions of styrene derivatives with additional substitution in the double bond have been described (Table 18).



(38)

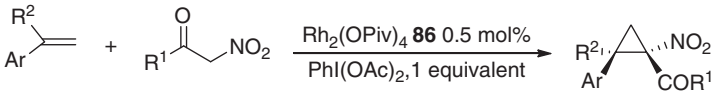
Table 18 Nonenantioselective cyclopropanations of styrenes with additional substitution in the double bond

Catalyst	R_1	R_2	*Ar*	R_3	R_4	R_5	*Alkene/diazoester*	*Yield (%)*	trans/cis	*References*
155	H	Et	Ph	CH_3	H	H	5/1	99	3:97	680
$Rh_2(TPA)_4$ **162**	Me	Et	Ph	CH_3	H	H	3/1	91	80:20	495
$Rh_2(TPA)_4$ **162**	Me	Et	Ph	Ph	H	H	3/1	99	–	495
$Rh_2(TPA)_4$ **162**	Bu	Et	Ph	CH_3	H	H	1/4	88	95:5	495
$Rh_2(OPiv)_4$ **86**	NO_2	Me	Ph	CH_3	H	H	5/1	91	97:3	492
$Rh_2(OPiv)_4$ **86**	NO_2	Me	Ph	Ph	H	H	5/1	97	–	492
$AgSbF_6$	Ph	Me	Ph	Ph	H	H	5–10/1	82	–	150
$AgSbF_6$	Ph	Me	Ph	H	H	Me	5–10/1	86	99:1	150
$AgSbF_6$	Ph	Me	Ph	H	Me	H	5–10/1	60	99:1	150
$AgSbF_6$	Ph	Me	Ph	H	H	Ph	5–10/1	54	99:1	150
$AgSbF_6$	Ph	Me	Ph	H	Ph	H	5–10/1	84	–	150
$AgSbF_6$	PhCH=CH	Me	Ph	Ph	–	–	5–10/1	56	–	150
$AgSbF_6$	PhCH=CH	Me	Ph	–	Me	–	5–10/1	65	99:1	150
$AgSbF_6$	PhCH=CH	Me	Ph	–	Ph	–	5–10/1	34	–	150

It is also possible to use carbene precursors alternative to diazo compounds with the advantage of a broad application and the reduction of safety risks regarding industrial application. In this regard, *in situ*-generated iodonium ylides allow for efficient preparation of 1-nitro-1-carbonylcyclopropanes in organic solvents, in water and under solvent-free conditions (Table 19).[492]

Table 19 Cyclopropanation with *in situ*-generated iodonium ylides

Ar	R_2	R_1	*Yield (%)*	trans/cis
Ph	H	*o*-Allyl	71	90:10
Ph	H	*o*-Benzyl	83	84:16
Ph	H	OPr^i	64	82:18
Ph	H	Ph	61	9:91
Ph	H	Ph	75	10:90
Ph	H	*c*-C_3H_5	72	72:28
Ph	H	OMe	83	92:8
Ph	Me	OMe	91	98:3
Ph	Ph	OMe	97	–
p-$MeOC_6H_4$	H	OMe	91	–
p-ClC_6H_4	H	OMe	87	91:9



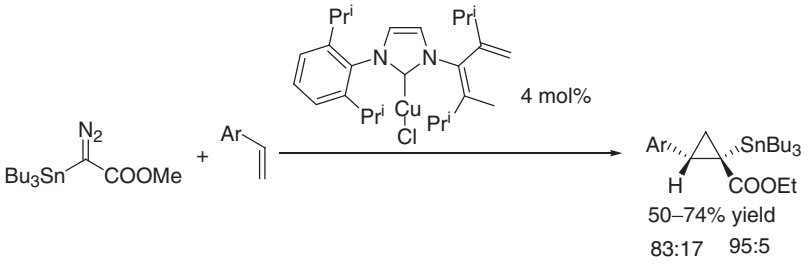
(39)

Some recoverable catalysts have been described for nonenantioselective cyclopropanations. Dirhodium (II) carboxylate complexes embedded into amino-functionalized SBA-15 behave as active, highly diastereoselective, and recyclable cyclopropanation catalysts. Thus, supported $(Rh_2(O_2CCF_3)_4$ was used four times in the reaction of styrene **10** with methyl phenyldiazoacetate **39** with a *cis*-selectivity of 99% in all cycles and yields decreasing from 89% to 64%.[369]

Cu-exchanged phosphotungstic acid is a reusable and simply obtained cyclopropanation catalyst, as shown in the reaction of ethyl diazoacetate **12** with styrene **10** and other alkenes, leading to high yields, up to 95%, but moderate *trans*/*cis* ratios, of up to 80:20. The solid is recovered for three of four runs with a minimal decrease in activity.[293]

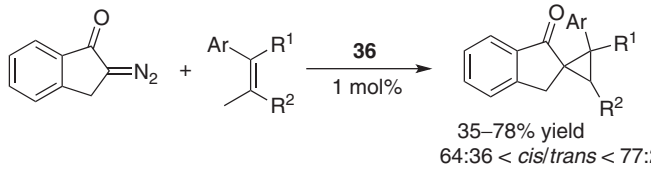
A soluble noncross-linked polystyrene-Ru catalyst promotes the reaction of ethyl diazoacetate **12** with styrene **10**, *p*-Cl-styrene **163,** and *p*-MeO-styrene **164**. Thus using 1% Ru and an alkene/diazocompound ratio of 2:1 yields between 85% and 91% and *trans*/*cis* ratios between 68/32 and 73/27 are achieved.[753]

A Cu(I)-NHC complex catalyzes the diastereoselective reaction of alkenes with (tributylstannyl)diazoacetates to stannyl cyclopropanes.[232]



(40)

Cyclic diazocompounds are used to obtain spirocyclopropanes, so 2-diazo-l-indanone **165** has been used in non-enantioselective reactions promoted by $Rh_2(OAc)_4$ **36** (1 mol%).[124]



(41)

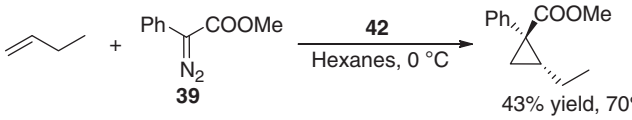
4.20.4.1.4.2 Open-chain alkenes

To our best knowledge, no cyclopropanation reactions of ketocarbenoids of ethylene or propylene have been reported, presumably due to the difficulties of handling such gases as reagents. It can be noted that cyclopropanation reactions between carbenoids bearing two different substituents and 1-alkenes (excepting ethylene) should lead to a diastereomixture of *cis*- and *trans*-cyclopropane derivatives.

4.20.4.1.4.2.1 Linear 1-alkenes

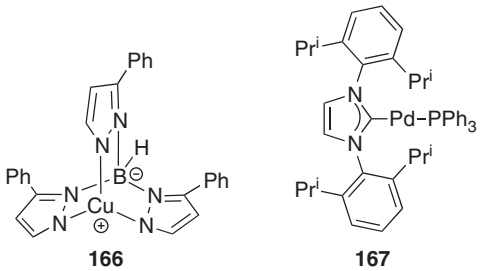
Many examples of reactions of linear 1-alkenes refer to enantioselective reactions carried out with chiral catalysts (see Section 4.20.4.1.5.2). Nevertheless, some examples will be presented herein, mainly in connection with diastereoselectivity issues.

1-Butene (bp: −6 °C) has been used in a cyclopropanation reaction with methyl phenyldiazoacetate **39** catalyzed by $Rh_2(S\text{-DOSP})_4$ **42** at 0 °C, affording the corresponding *trans*-cyclopropane with total diastereoselectivity.[754]



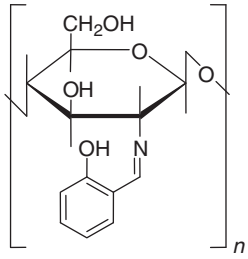
(42)

Trans/*cis*-stereoselectivities close to 1:1 are usually obtained in reactions of 1-hexene with simple diazoacetic esters using some nonchiral catalysts, such as the trispyrazolylborate–Cu(I) catalyst **166** (56:44)[755] or the imidazole–Pd(0) catalyst **167** (60:40).[99] Interestingly, the stereoselectivity of such reactions can be tuned by changing the catalyst or the diazo compound. Thus, a larger *trans*-preference can be obtained using a bulky diazoacetic ester (2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168**, 93% yield, *trans*/*cis* = 75:25).[135] Instead, a *cis*-preference (as well as very high enantioselectivities) can be obtained by using chiral Ru complexes of (iminophosphoranyl)ferrocenes (79% yield, *trans*/*cis* = 16:84, 92% *ee trans*, 94% *ee cis*).[628]



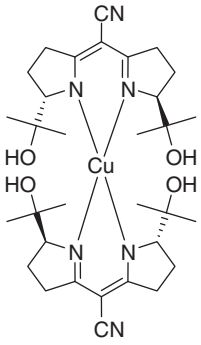
High *trans*/*cis*-selectivities can be obtained in cyclopropanation reactions between 1-heptene and diazoacetic esters by an adequate catalyst selection. Thus, a modest 59:41 selectivity has been obtained in the reaction of ethyl diazoacetate **12** catalyzed by $Rh_2(OAc)_4$ **36** at 50 °C (50% yield).[381] A minor improvement can be achieved using some copper catalysts, such as the chitosan–Schiff base copper complex **169** (*trans*/*cis* = 64:36)[756] or a Cu–semicorrin (**170**) (*trans*/*cis* = 72:28).[381] A further diastereoisomeric ratio increase can be achieved using some Ru catalysts, such as **171** (83:17)[129] or **145**, in combination with the use of (−)-menthyl

diazoacetate **144** (*trans*/*cis* = 92:8, 54% yield).[588] In contrast, only a modest selectivity increase can be obtained using *tert*-butyl diazoacetate **133** instead of methyl diazoacetate **54** (71:29 vs. 64:36, respectively, for the **169**-catalyzed reaction).[756]



169

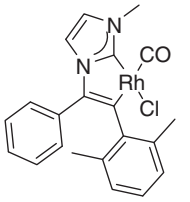
$Cu(OAc)_2 \cdot H_2O$



170

A moderate *trans*/*cis*-selectivity has been obtained for the reaction of 1-octene **28** with ethyl diazoacetate **12** with Bu^{t}DAX-Cu **172** (68:32, 93% *ee trans*, 93% *ee cis*, 75% yield) and Bu^t-click-DAX-Cu **173** (68:32, 90% *ee trans*, 86% *ee cis*, 54% yield).[420] A low stereoselectivity (*trans*/*cis* = 57:43, 68% yield) was obtained using $PtCl_4$ as a catalyst at 80 °C.[681] Reaction of 1-octene **28** with a chiral Co(II) complex (**174**) leads to cyclopropanes with low *trans*/*cis*-diastereoselectivity (64:36), but high enantioselectivity in *trans*-cyclopropanes (97% *ee trans*, 18% *ee cis*).[757] The use of *tert*-butyl diazoacetate **133** with a bipy-CuOTf catalyst (**175**) allows a selectivity increase (*trans*/*cis* = 85:15, 91% *ee trans*, 65% yield).[332] Cyclopropanation of 1-octene **28** with ethyl diazoacetate **12** in the presence of $Rh_2(OAc)_4$ **36** immobilized in $[bmim]PF_6$ leads to 70% yield, 60:40 *trans*/*cis*.[742] Instead, the analogous reaction achieved in the presence of a glycosylated Ru–porphyrin **176** induces a very high *trans*-preference (*trans*/*cis* = 89:11, 78% yield).[608]

Interestingly, a *cis*-preference is found for the reactions catalyzed by some polypyrazolylborate–Cu complexes (up to *trans*/*cis* = 23:77, 62% yield),[366] Rh catalyst activated by silver, (**177**)-AgOTf (22:78, 60% yield),[548] **177**/NaBArf (*trans*/*cis* = 25:75, 95% isolated yield),[752] Ir-salen (**179**) (2:98, 98% *ee cis*),[648] Ru-iminophosphoranylferrocenes (28:72, 98% *ee cis*, 74% *ee trans*).[628]



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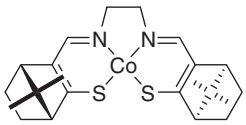

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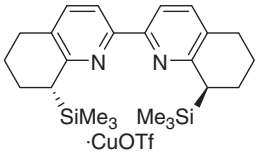

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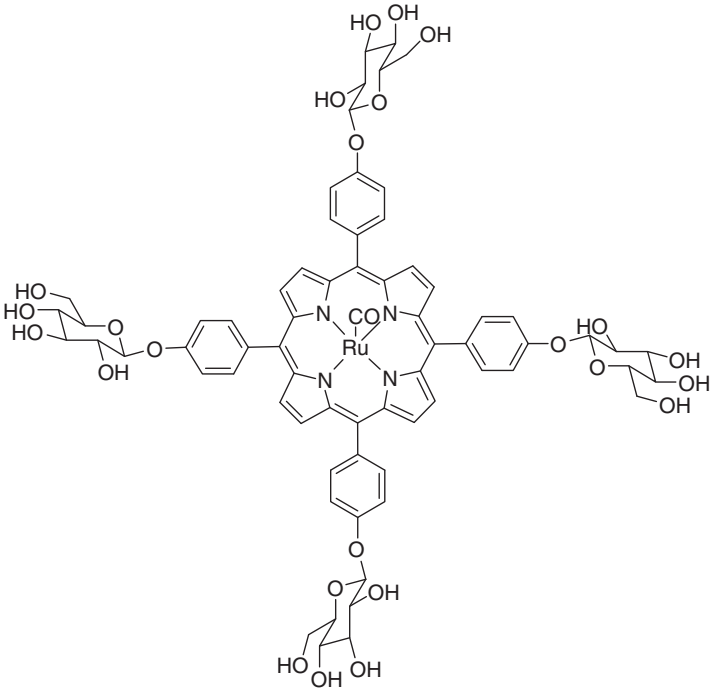
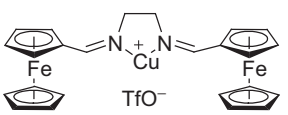


180

1-Decene can be cyclopropanated with ethyl diazoacetate **12** in the presence of a number of catalysts, such as FcNN-CuOTf (**181**) (*trans*/*cis* = 68:32, 66% yield),[758] the Ru–arene complex **182** (*trans*/*cis* = 58:42, 42% yield),[585] and a triiminophosphorane-$Cu(OTf)_2$ (*trans*/*cis* = 62:38, 68% yield).[680]



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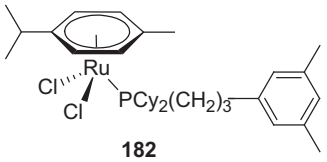


182

A number of catalysts have been tested for the 1-dodecene+ethyl diazoacetate **12** cyclopropanation reaction, usually leading to low *cis*-preferences and modest yields, such as a Ru-arene complex (*trans*/*cis* = 58:42, 42% yield),[585] $PtCl_4$ (*trans*/*cis* = 57:43, 72% yield),[681] a Rh(I)-carborane phosphine (*trans*/*cis* = 60:40, 73% yield).[545] The highest yield for this reaction has been obtained using $Cu(OTf)_2$ in hexafluoroisopropanol (HFIP) (98% yield, *trans*/*cis* = 41:59).[488]

4.20.4.1.4.2.2 Linear internal alkenes

As in the case of linear 1-alkenes, the enantioselective reactions with these substrates are mainly described later (see Section 4.20.4.1.5.2), but some examples will be presented herein, mainly in connection with diastereoselectivity issues. Internal alkenes display reactivity issues also related with the absolute configuration of the double bond.

Thus, reactivity differences between (*Z*)- and (*E*)-2-butene have been observed in the reactions with ethyl nitrodiazoacetate **183** catalyzed by $Rh_2(OAc)_4$ **36**. Thus, whereas a 65% cyclopropane yield (*trans*/*cis* = 20:80) has been found for (*Z*)-2-butene, the ene-reaction product was only observed when the *trans*-analog was used.[201] Acceptable yields have been obtained under $Rh_2(OAc)_4$ **36** catalysis by (*Z*)-2-butene **90** with ethyl (65% yield, *trans*/*cis* = 4:1) and *tert*-butyl nitrodiazoacetate (50% yield, *trans*/*cis* = 9:91) as well as nitroacetophenone (45% yield, *trans*/*cis* = 91:9).[200]

(*Z*)-2-pentene is slightly more reactive than the corresponding (*E*)-isomer in catalyzed cyclopropanation reactions, presumably due to the less hindering shape of the former. Thus, a better yield (75% vs. 69%) has been obtained in the $Rh_2(OAc)_4$ **36**-catalyzed reactions with the isolated Meldrum's acid-derived phenyliodonium ylide **109**.[262]

(*Z*)-2-pentene has also been used in some cyclopropanation reactions with iodonium ylides catalyzed by $Rh_2(S\text{-nttl})_4$ **107**. Moderate yields (50–53%) and low enantioselectitivies (25–31% *ee*) were obtained by using *in situ*-obtained phenyliodonium ylides from Meldrum's acid **109** and dimethyl malonate.[759] Instead, high yield (93%) and enantioselectivity (63% *ee*) were obtained using the isolated Meldrum's acid phenyliodonium ylide.[262]

(*E*)-2-pentene has reacted with ethyl diazoacetate **12** in the presence of $Rh_2(OAc)_4$ **36** to afford the corresponding cyclopropanes with 43% yield (*trans*/*cis* = 56:44).[381]

Both (*E*) and (*Z*)-2-hexenes have been used in cyclopropanation reactions with ethyl diazoacetate **12** catalyzed by $TP^{(CF3)2}Na$/CuCl, with acceptable yields and good *cis*-selectivities (*E*: 54% yield, *trans*/*cis* = 26:74; *Z*: 54% yield, *trans*/*cis* = 33:67).[366]

(*E*)-2-octene reacted with the methyl acetate-diphenylphosphonium ylide in the presence of Cu(pentylacetylacetonate)$_2$ with 58% yield.[254] Glycine methyl ester has been used as a diazo precursor in the TPPRhI-catalyzed reaction with 59% yield.[760]

(*Z*)-2-decene reacted with TPPRhI using glycine methyl ester hydrochloride to afford the corresponding cyclopropane with 52% yield.[760]

(*Z*)-3-hexene reacted with ethyl diazoacetate **12** in the presence of methylrhenium trioxide to afford the corresponding cyclopropane in 63% yield.[691]

The *Z* isomer of 4-octene is more reactive in catalyzed cyclopropanation reactions than the corresponding *E* analog. Thus, alternative reactions of both the stereoisomers with dimethyl diazomalonate under $Rh_2(OAc)_4$ **36** catalysis in acetonitrile has led to 78% and 73% yields, respectively,[49] whereas the use of $Rh_2(esp)_2$ **71** leads to 41% and <5% yields, respectively.[761] (*Z*)-4-octene has been used as a probe for the multiplicity of di(methoxycarbonyl)carbene photochemically generated from several sulfonium ylides. The largest *cis* stereochemical control (93.5% yield in *cis*-cyclopropanes, *trans*/*cis* = 3:97) has been obtained from the 2-bromothiophene derivative.[49] (*E*)-4-octene has been cyclopropanated with ethyl diazoacetate **12** using methyltrioxorhenium as a catalyst in 59% yield.[691]

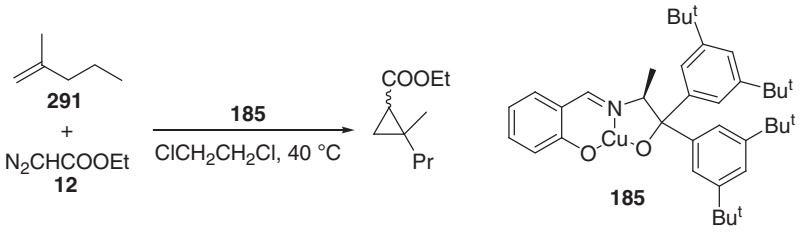
7-Tetradecene reacted with glycine methyl ester and sodium nitrite under TPPRhI catalysis to afford the corresponding cyclopropane in 55% yield.[760]

4.20.4.1.4.2.3 Branched alkenes

Branched alkenes may present reactivity problems, above all in the case of tetrasubstituted carbon–carbon double bonds. As in the precedent cases, they also display stereoselectivity issues. In this section we will only concentrate on diastereoselectivities. For the discussion on enantioselectivity, see Section 4.20.4.1.5.2.

2-Methylpropene[762] **89** has been used in $Rh_2(OAc)_4$ **36**-catalyzed cyclopropanation reactions with a number of reactants: ethyl **12**(50% yield) and *tert*-butyl diazoacetate **133** (75% yield), nitroacetophenone (58% yield),[200] and Oppolzer's sultam-derived α-diazoamide (83% yield, 90% *de*).[172] 2-Methylpropene **89** reacts with menthyl diazoacetate **144** in the presence of Cu(I)-(*R*)-BINIM-DC **184** to afford the corresponding cyclopropane mixture with 66% yield, 65% *de*.[763]

2-Methyl-1-pentene **291** has been reacted with ethyl diazoacetate **12** in the presence of a Schiff base-copper catalyst (**185**) to afford the corresponding cyclopropanes with low selectivity (*trans*/*cis* = 53:47).[311]



(43a)

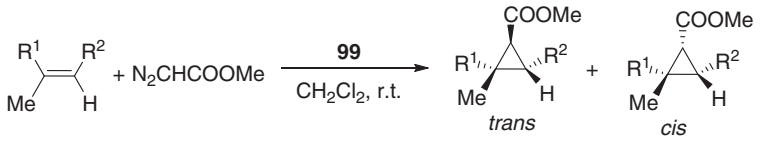
2-Methyl-1-octene **186** has been made to react with ethyl diazoacetate **12** in the presence of salen–Ir complex **179** leading to a slight *cis*-preference (65% yield, *trans*/*cis* = 44:56, 99% *ee cis*).[649]

3-Methylenepentane (2-ethyl-1-butene, **187**) reacts with methyl 2-diazo-3-(3-methyl-1*H*-indol-1-yl)-3-oxopropanoate **188** in the presence of $Rh_2(esp)_2$ **71** to afford the corresponding cyclopropane in 50% yield.[181]

High *trans*/*cis*-selectivities are obtained as a rule in catalyzed cyclopropanation reactions of monosubstituted alkenes bearing a hindering substituent, such as 3,3-dimethyl-1-butene **189**. Thus, this substrate has been used in a reaction with menthyl diazoacetate **144** catalyzed by Rh_2(*S*-MEPY)$_4$ **190**, with good *trans*/*cis*-selectivity (71:29), and better enantioselectivities (91% *ee cis*, 65% *ee trans*).[764] A higher diastereoselectivity has been obtained in a reaction involving ethyl diazoacetate **12** in the presence of $Rh_2(O_2PMe_2)_4$ (**191**, *trans*/*cis* = 83:17).[765] Very high diastereostereoselectivities have been achieved in the presence of $Rh_2(OAc)_4$ **36** using hampering diazoacetic esters (Et, 75%; 2,3,4-trimethylpentan-3-yl, 84% *trans*; 3-isopropyl-2-methylhept-3-anyl, 89% *trans*; 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168**, 93% *trans*).[135]

Both *cis*- and *trans*-cyclopropane products can be obtained in catalyzed reactions of 2-methyl-2-butene **51** with diazoacetic esters. A slight *trans*-preference is observed as a rule in $Rh_2(OAc)_4$ **36**-catalyzed reactions (60% for ethyl diazoacetate (**12**), though a significant diastereoselectivity increase can be obtained by using 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168** (96% *trans*).[135] In contrast, remarkable *cis*-preferences (84–87% are found for the reactions with alkyl (Me, Et, and Bu^t) diazoacetates in the presence of $Ru_2(OAc)_2(CO)_4$ **99**.[144]

The application of **99** to cyclopropanation reactions of some trialkyl ethylenes showed a clear *cis*-preference (**Table 1**). Thus, trimethylethylene (2-methyl-2-butene **51**) shows a 86:14 *cis*/*trans* ratio (equation 43b, **Table 20**).[144] In contrast, lower stereoselectivities (79:21) has been obtained using some diruthenium saccharinate complexes.[766]



(43b)

Table 20 Results of the reaction between different trisubstituted alkenes with methyl diazoacetate **54** catalyzed by **99**

R^1	R^2	*Yield (%)*	trans/cis
Me	Me	61	14:86
–$(CH_2)_4$–		72	29:71
Me	CH_2CCl_3	55	16:84
Me	Cl	20	9:91
Me	CH=CMe_2	91	10:90
Me	CH=CCl_2	30	17:83

Tetrasubstituted alkenes show a very low reactivity in typical intermolecular cyclopropanation reactions because of steric interactions. As an example, a very low yield (7%) has been obtained in the 1,2,3,4,5,6,7,8-octahydronaphthalene **192**+ethyl diazoacetate **12** reaction in the presence of $[Cu(MeCN)_4]^+$**193**.[767] In contrast, a good yield for this reaction (56%) has been obtained when a cation radical initiator was used.[768]

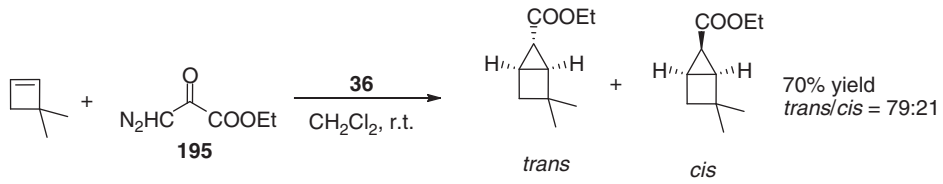
A similar behavior can be observed for tetramethylethylene **15**. Thus, low yields are typically found in the reactions with ethyl diazoacetate **12** in the presence of common catalysts (such as Ru (18–47%),[571] $Cu(acac)_2$ **110** under microwave irradiation (31%).[769] Highly reactive catalysts, such as Cu–salen (up to 82%),[299] methyltrioxorhenium **194** (57%)[691] or the Cu–ferrocenyldiimine **181** (78%),[758] are required for obtaining good yields. Interestingly, the best yields in cyclopropanation reactions

involving tetramethylethylene have been obtained by using ketocarbenes generated under thermal (96%)[39] or photochemical conditions (98%).[41]

4.20.4.1.4.3 Cycloalkenes

4.20.4.1.4.3.1 Cyclobutenes

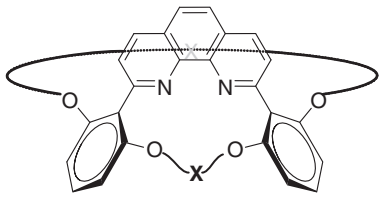
3,3-Dimethylcyclobutene reacts with methyl diazopyruvate **195** in the presence of $Rh_2(OAc)_4$ **36** to afford the corresponding cyclopropane mixture in 70% yield.[770]



(44)

4.20.4.1.4.3.2 Cyclopentene

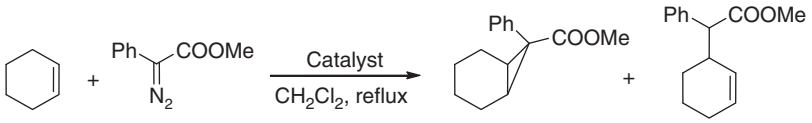
Cyclopentene was cyclopropanated with the dimethyl malonate phenyliodonium ylide **196** in the presence of $Rh_2(OAc)_4$ **36** to yield a pure cyclopropane in 91% yield.[771] Significant variations were observed on the *trans*/*cis*-selectivity for the reaction between cyclopentene and ethyl diazoacetate **12** catalyzed by CuOTf **78** depending on the presence of concave ligands. Thus, the use of the concave ligand **197** allows raising the 77:23 selectivity to a 98:2 ratio.[354]



X = $-(CH_2CH_2O)_2CH_3$ $CH_3(OCH_2CH_2)-$: **197**
X = $-(CH_2CH_2O)_2CH_2-$: **198**
X = $-(CH_2CH_2O)_3CH_2-$: **199**

4.20.4.1.4.3.3 Cyclohexene

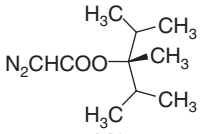
Although high yields are usually obtained in the $Rh_2(OAc)_4$ **36** reactions of cyclohexene **49** with diazoacetic esters, poorer results are achieved in processes favoring the C–H carbene insertion reaction. Thus, the reaction of dimethyl diazomalonate **65** under $Rh_2(OAc)_4$ **36** catalysis leads to a cyclopropane/C–H insertion product in a 62:38 ratio (96% yield), whereas a 91:9 ratio is found with $Cu(acac)_2$ (**110**, 57% yield).[709] A high yield (88%) and diastereoselectivity (97% *trans*) was found in the cyclohexene **49** +methyl phenyldiazoacetate **39** reaction by using $AgSbF_6$ **201**, whereas the use of $Rh_2(OAc)_4$ **36** led to a preference for the C–H carbene insertion product (equation 45).[150]



(45)

Catalyst	Combined yield (%)	Cyclopropanation/C-H insertion
$AgSbF_6$	88	>94:6
$Rh_2(OAc)_4$ (**36**)	44	31:69

Both *trans*- and *cis*-cyclopropanes can be obtained from cyclopropanation reactions of cyclohexene **49** with diazoacetic esters. Moderate diastereoselectivies are obtained in reactions catalyzed by common catalysts ($Rh_2(OAc)_4$ **36**, 78% *trans*[772]; CuCl, 60.4% *trans*).[773] Interestingly, these stereoisomeric ratios can be increased by using either other catalyst, such as $Rh_2(NHCOMe)_4$ (89% *trans*), or a bulkier diazo compound, such as 2,3,4-trimethyl-3-pentyl diazoacetate **142** (86% *trans* under $Rh_2(OAc)_4$ **36** catalysis).[135]

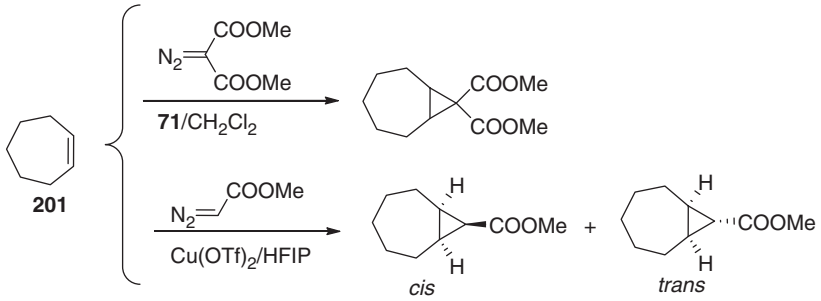


142

A total stereoselectivity for the cyclohexene **49**+ethyl diazoacetate **12** cyclopropanation reaction has been achieved by using some MOF derived from copper and gold. Thus, 100% *trans*-selectivity (50% yield) was obtained in a reaction in the presence of IRMOF-3-SI-Au.[151]

4.20.4.1.4.3.4 Cycloheptene

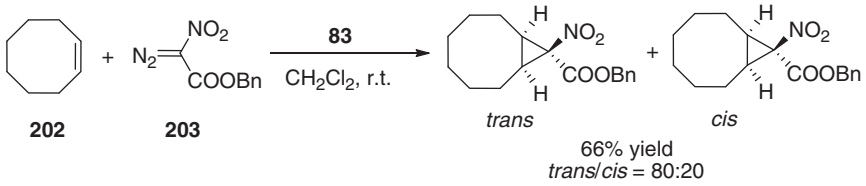
Cycloheptene **201** reacts with dimethyl diazomalonate under $Rh_2(esp)_4$ **71** catalysis with 72% yield.[761] Compound **201** has been used as a substrate in the reaction with ethyl diazoacetate **12** in $Cu(OTf)_2$/HFIP solution in 82% yield (*trans*/*cis* = 20:80) (**Scheme 22**).[488]



Scheme 22

4.20.4.1.4.3.5 Cyclooctene

Cyclooctene **202** reacts with benzyl nitrodiazoacetate **203** in the presence of $Rh_2(octanoate)_4$ **83** to afford the corresponding cyclopropane mixture (66% yield, *trans*/*cis* = 80:20) (**Scheme 23**).[202] A very high stereoselectivity (*trans*/*cis* = 98:2) was obtained in the reaction between **202** and methyl phenyldiazoacetate **39** in the presence of a $Cu_3(BTC)_2$-based MOF (70% yield).[151]



202 **203** *trans* *cis*

66% yield
trans/*cis* = 80:20

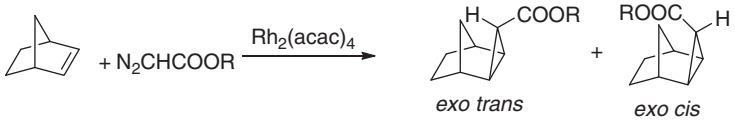
Scheme 23

4.20.4.1.4.3.6 Norbornene

A complex mixture of cyclopropanes depending on several stereoisomeric features (*endo*/*exo*, *trans*/*cis*, both enantiomers) can be obtained from the reactions of norbornene **27** with nonsymmetric ketocarbenoids. Interestingly, only two diastereoisomeric products (*exo trans* and *exo cis*) are usually obtained in such reactions.[677]

An *exo trans*-preference is usually observed in norbornene **27**+ethyl diazoacetate **12** reactions, as those catalyzed by CuCl (*trans*/*cis* = 71:29),[773] $Pd(OAc)_2$ (*trans*/*cis* = 71:29, 95% yield),[677] or a dicopper-substitute silicotungstate (*trans*/*anti* = 84:16, 88% yield).[295] Instead, an *exo-cis* preference can be achieved by using RhTDCPPCl (**204**, *trans*/*anti* = 22:78, 50% yield).[773]

A high stereoselectivity (92:8) can be achieved by using 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168** in the presence of $Rh_2(OAc)_4$ **36**, whereas a more modest (82:18) ratio is obtained with ethyl diazoacetate **12** (equation 46).[135]



exo trans *exo cis*

R = 2,6-di-*tert*-butyl-4-methylphenyl: *exo trans*/*exo cis* = 92:8
R = Et: *exo trans*/*exo cis* = 82:18

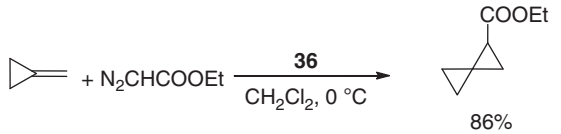
(46)

Norbornene **27** reacts with *tert*-butyl cyanodiazoacetate **205** in the presence of **130** (66% yield, ratio = 83:17).[194]

4.20.4.1.4.4 Alkylidenecycloalkanes

4.20.4.1.4.4.1 Alkylidenecyclopropanes

High yields can be obtained in $Rh_2(OAc)_4$ **36**-catalyzed cyclopropanation reactions of alkylidenecyclopropanes with diazo compounds, such as methylenecyclopropane **206**+ethyl diazoacetate **12** (86%),[444] bicyclopropylidene **207**+ethyl diazoacetate **12** (77%),[444] or **206**+ethyl nitrodiazoacetate **183** (85%).[774]



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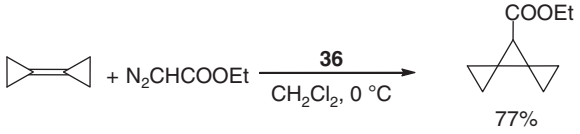

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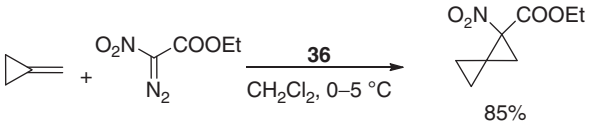
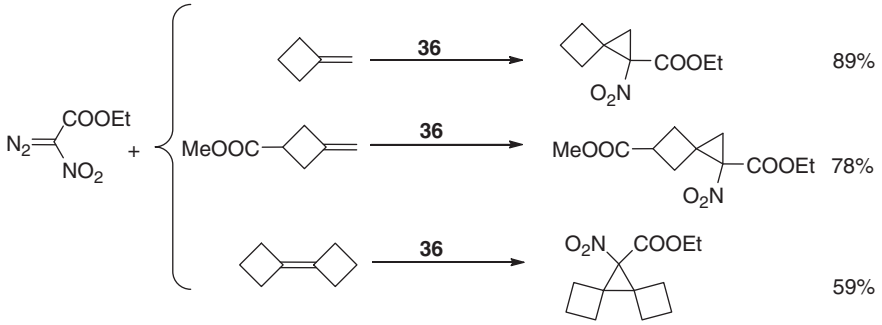


(49)

4.20.4.1.4.4.2 Alkylidenecyclobutanes

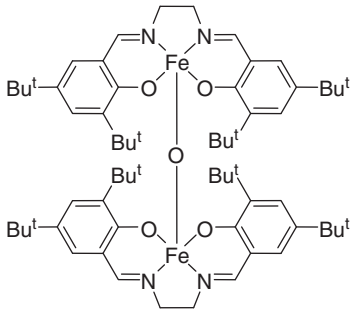
Good yields have been obtained in the cyclopropanation reactions of methylenecyclobutane **208** (89%),[203] methyl 3-methylenecyclobutanecarboxylate **209** (78%), and bicyclobutylidene **210** (59%) with ethyl nitrodiazoacetate **183** using $Rh_2(OAc)_4$ **36** as a catalyst (**Scheme 24**).[203]



Scheme 24

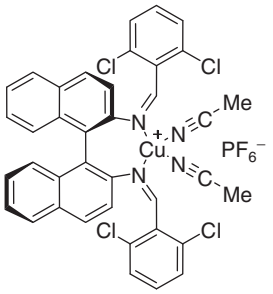
4.20.4.1.4.3 Alkylidenecyclohexanes

Methylenecyclohexane **211** reacts with ethyl diazoacetate **12** in the presence of the Fe–salen complex **212** (88% yield).[646] Compound **211** reacted with glycine methyl ester **213** and sodium nitrite in the presence of TPPRhI **119** to afford the corresponding cyclopropane in 64% yield.[760]



212

Compound **211** reacted with menthyl diazoacetate **144** in the presence of 1,1′-binaphthyl-*N*,*N*′-bis(2,6-dichloro-benzylidene)-2,2′-diamine (1)–Cu complex **214** to yield the corresponding cyclopropanes with 90% yield and 57% *ee*.[775]



214

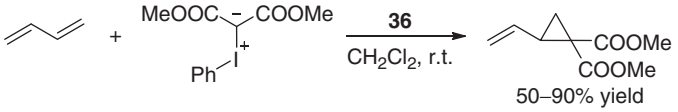
β-Pinene **215** reacted with ethyl diazoacetate **12** catalyzed by $Pd(OAc)_2$/CuI affording the corresponding product as a mixture of four diastereomers, which were hydrolyzed in a 65–75% overall yield.[776]

Good yields are obtained in the $Rh_2(OAc)_4$ **36**-catalyzed reactions of 2-methyleneadamantane with ethyl nitrodiazoacetate **183** (65%)[777] or some substituted 3-diazoindolinones (up to 89%).[778]

4.20.4.1.4.5 Dienes

4.20.4.1.4.5.1 1,3-Butadiene

Low yields and selectivities are usually obtained in cyclopropanation reactions of 1,3-butadiene **216** with simple diazoacetates using simple catalysts (ethyl diazoacetate **12**, $Rh_2(OAc)_4$ **36**, 36% yield, *trans*/*cis* = 55:45[381]; $Cu(OAc)_2$/2,4-lutidine/$ZnCl_2$, methyl diazoacetate **54**: 49% yield, *trans*/*cis* = 57:43).[779] Better results have been obtained using phenyliodonium ylides bearing two electron-withdrawing groups (dimethyl malonate-derived ylide, $Rh_2(OAc)_4$ **36**: 50–90% yield[780]; methyl nitroacetate-derived ylide, Cu-**217**, 84% yield, *dr* = 82:18, 90% *ee*).[260]



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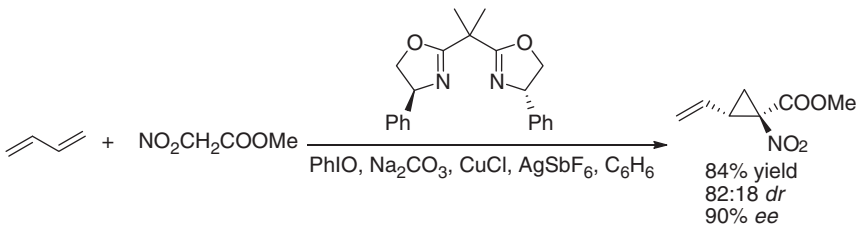
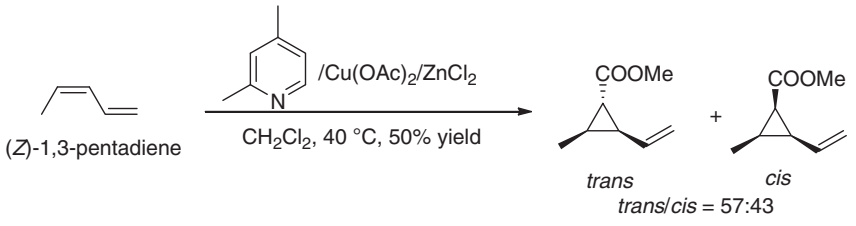


(51)

4.20.4.1.4.5.2 1,3-Pentadiene

Two differently substituted C=C bonds are present in 1,3-pentadienes. The reaction with methyl diazoacetate **54** under $Cu(OAc)_2$/2,4-lutidine/$ZnCl_2$ catalysis showed a preference for the reaction of the most substituted C=C bond. Reactions of both (*Z*) and (*E*)-isomers of 1,3-pentadiene led to 50% yield (*trans*/*cis* = 57:43).[779]



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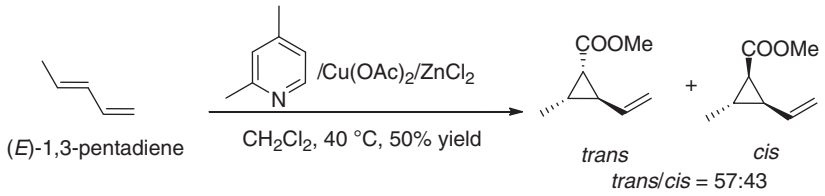
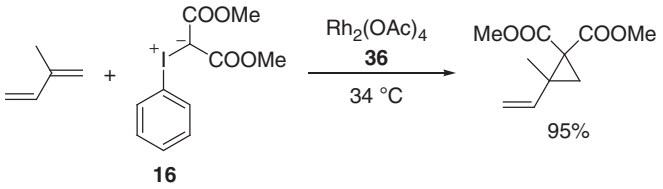


(53)

4.20.4.1.4.5.3 Isoprene

A significantly larger reactivity of the disubstituted C═C bond relative to the monosubstituted analog has been observed in a number of catalyzed cyclopropanation reactions of isoprene **218**. Thus, **218** was cyclopropanated with dimethyl malonate-phenyliodonium ylide **16** in the presence of $Rh_2(OAc)_4$ **36** to afford the corresponding disubstituted cyclopropane in 95% yield.[771]

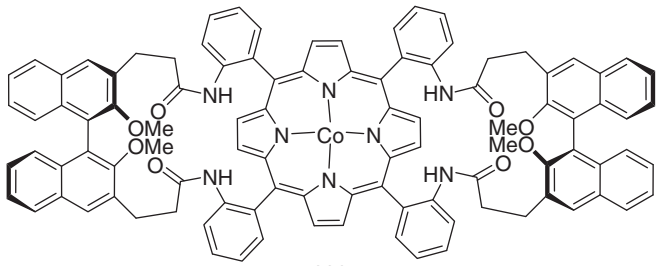


(54)

Both regio- and diastereoselectivities of cyclopropanation reactions involving nonsymmetric ketocarbenoids are strongly dependent on the catalyst. Thus, the use of the mixture $Cu(OAc)_2$/2,4-lutidine/$ZnCl_2$ allowed obtaining a high regioselectivity (disubstituted/monosubstituted = 52:9, *trans*/*cis* = 57:43, 61% yield).[779] Instead, the use of **99** led to a high stereoselectivity for the minor regioisomeric reaction product (disubstituted, 56%, *trans*/*cis* = 48:52; monosubstituted, 36%, *trans*/*cis* = 71:29, 92% yield).[222]

4.20.4.1.4.5.4 2,3-Dimethylbutadiene

2,3-Dimethylbutadiene **219** has been reacted with ethyl diazoacetate **12** by using a number of catalysts, such as **220** (90% yield, *trans*/*cis* = 84:16),[666] copper pyrazolate complexes (88–89% yield, *trans*/*cis* ≤60:40),[781] and $Cu_2(L2)_2(OTf)_2$ (71% yield, *trans*/*cis* = 51:49).[782] Low enantioselectivities are obtained in the case of chiral catalysts.

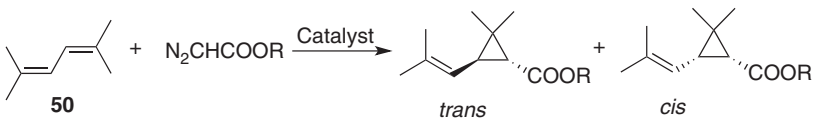


220

Compound **219** also reacted with iodonium ylides, such as dimethyl malonate-phenyliodonium ylide **16** under $Rh_2(OAc)_4$ **36** catalysis (88% yield)[771] or methyl nitroacetate-derivative in the presence of a Cu-**217** catalyst (54% yield, 95:5 *dr*, 85% *ee*).[260]

4.20.4.1.4.5.5 2,5-Dimethyl-2,4-hexadiene

A special interest has been paid to the cyclopropanation reaction of 2,5-dimethyl-2,4-hexadiene **50** with diazoacetic esters as a key step in the synthesis of chrysanthemic acid, a natural insecticide. High diastereoselectivities were obtained by using hindered diazoacetic esters, such as 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168** under Rh_2(acetamidate)$_4$ catalysis (75% yield, *trans*/*cis* = 98:2)[135] or dicyclohexylmethyl diazoacetate **221** in the presence of $Cu(MeCN)_4ClO_4$ (78% yield, 95:5 *trans*/*cis*).[410] Although ethyl **12** and *tert*-butyl **133** diazoacetates with usual catalysts have led to good yields as a rule, diastereoselectivities are often only moderate (60–80% *trans*).[317,318]

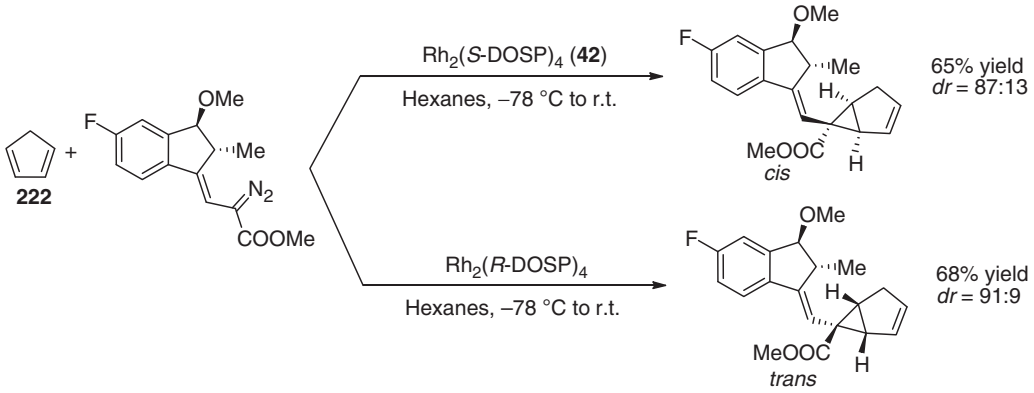


For details on the enantioselective version of these reactions, see Section 4.20.4.1.5.2.1.

4.20.4.1.4.5.6 Cyclopentadiene

Cyclopentadiene **222** was monocyclopropanated with dimethyl malonate-phenyliodonium ylide **16** under $Rh_2(OAc)_4$ **36** catalysis in 99% yield.[771]

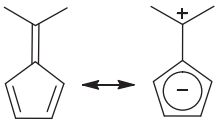
Compound **222** can be monocyclopropanated by using a number of alkylidene indane-derived diazoacetic esters at low temperatures leading to a preference for the *cis*-divinyl cyclopropanes (**Scheme 25**).[783] Heating of these stereoisomeric reaction products induced a Cope rearrangement.



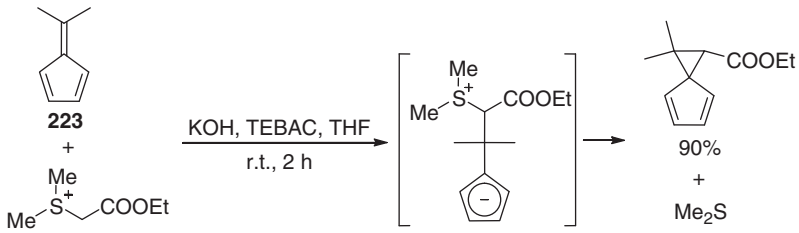
Scheme 25

4.20.4.1.4.5.7 Dimethylfulvene

A significant difference between endocyclic and exocyclic C=C bonds of 6,6-dimethylfulvene **223** can be inferred from resonance forms. Thus, whereas endocyclic bonds are electron-rich, the exocyclic bond is electron poor. As a consequence, regioselectivity of the cyclopropanation reaction of **223** can be controlled by means of the reaction conditions. Thermal reaction with an ylide leads to the regioselective cyclopropanation of an exocyclic C=C bond,[784] presumably due to the high stability of the intermediate involving a cyclopentadienide anion.

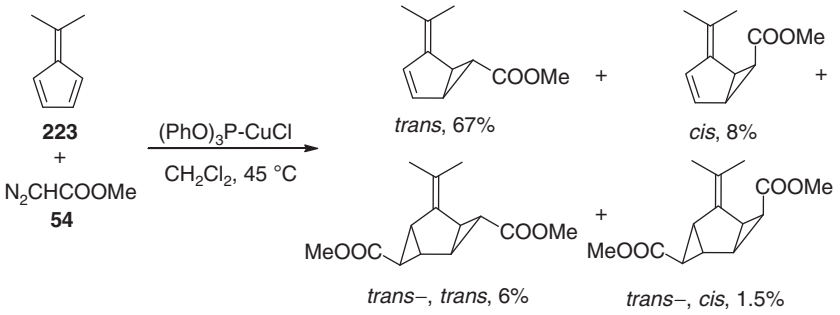


Although the most typical substrates in cyclopropanation reactions through zwitterions are olefins bearing electron-withdrawing substituents, fulvenes can also be used,[784] presumably due to the high stability of the zwitterionic intermediate bearing a cyclopentadienide anion (**Scheme 26**).



Scheme 26

Instead, endocyclic C=C bonds of **223** are much more reactive than exocyclic ones in catalyzed cyclopropanation reactions. Thus, only endocyclic C=C bonds of **223** are attacked by dimethyl malonate-phenyliodonium ylide **16** in the presence of $Rh_2(OAc)_4$ **36** (71% yield).[771] Furthermore, two stereoisomers (*endo* and *exo*) can be obtained in cyclopropanation reactions involving an endocyclic C=C bond of **223**. Thus, the reaction of ethyl diazoacetate **12** in the presence of $CuSO_4$ **112** led to an 86:14 *trans*/*cis* ratio (72% yield).[785] Furthermore, dicyclopropanated products can also be formed in cyclopropanation reactions of **223**, such as those observed in the reaction with methyl diazoacetate **54** in the presence of $(PhO)_3P$-CuCl (**224**, 82.5% overall yield) (equation 55).[786]

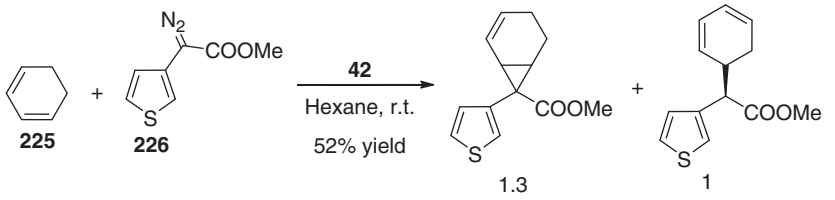


(55)

4.20.4.1.4.5.8 1,3-Cyclohexadiene

An almost quantitative monocyclopropanation reaction was achieved by using 1,3-cyclohexadiene **225** and dimethyl malonate-phenyliodonium ylide **16** under $Rh_2(OAc)_4$ **36** catalysis.[771] The *exo* monocyclopropanated product can be obtained by using ethyl diazopyruvate **68** (66% yield after chromatographic purification) under $Rh_2(OAc)_4$ **36**.[787]

The reaction of **225** with methyl (3-thiophenyl)diazoacetate **226** under $Rh_2(S\text{-DOSP})_4$ **42** catalysis led to a mixture of reaction products (cyclopropane, 1.3; C–H insertion product, 1; 53% combined yield).[166]



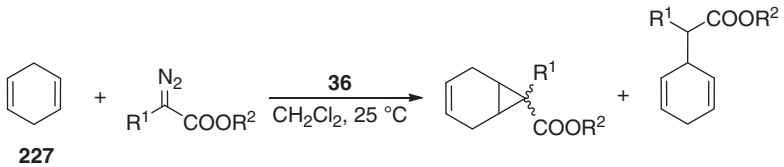
(56)

4.20.4.1.4.5.9 1,4-Cyclohexadiene

Because of the occurrence of four doubly allylic hydrogen atoms in the 1,4-cyclohexadiene **227** molecule, cyclopropanation of such a substrate can be affected by the competition with C–H insertion reaction (**Table 21**, see also Section 4.20.4.1.1.3).[709] Although a highly efficient cyclopropanation under **36** catalysis can be carried out with ethyl diazoacetate **12**, a more modest cyclopropane yield is obtained with dimethyl diazomalonate **11**. Instead, no significant cyclopropanation was observed when donor–acceptor diazo compounds were used (**Table 21**).

Table 21 Results of the reaction between 1,4-cyclohexadiene and some diazoesters by using **36** as a catalyst[709]

R^1	R^2	*Yield (%)*	*Cyclopropanation/C–H insertion*
H	Et	90	>98:2
COOMe	Me	63	34:66
Me	Et	82	<2:98
Ph	Me	95	<2:98



(57)

4.20.4.1.4.5.10 Cyclooctadienes

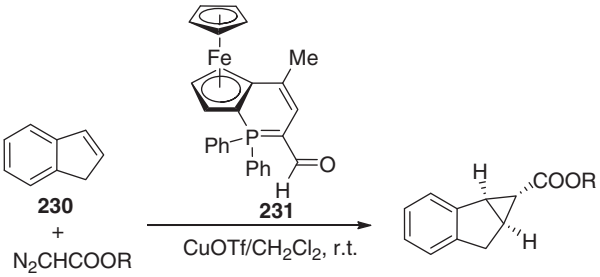
1,3-Cyclooctadiene **228** can be cyclopropanated using methyl diazoacetate **54** in the presence of $Rh_2(OAc)_4$ **36**. The monocyclopropanated product was obtained in 51% yield, whereas the dicyclopropanated product was formed in 1% yield.[788] The reaction of **228** with ethyl diazoacetate **12** under $[Rh(PE\text{-}CO_2)_2]_2$ catalysis afforded 72% yield (*trans*/*cis* = 57:43).[550] The reaction of 1,3-cyclooctadiene **228** with phenyliodonium bis(methoxycarbonyl)methylide **16** under $Rh_2(OAc)_4$ **36** catalysis afforded the corresponding cyclopropane in 58% yield.[771]

The dropwise addition of ethyl diazoacetate **12** with a large excess of 1,5-cyclooctadiene **229** in the presence of $Rh_2(OAc)_4$ **36** afforded a mixture of monocyclopropanes (*trans*/*cis* = 67:33), which was separated by chromatography on silica gel (combined yield, 76%).[789] However, the reaction with ethyl diazoacetate **12** with binuclear Cu catalysts (62–70% yields no dicyclopropanated product, *trans*/*cis* = 68:32).[790] Compound **229** reacts with 3-diazo-1-alkylindolinones by using CuOTf **78** (R = Me, 79% yield; R = Bn, 80% yield), whereas no reaction was observed with the methyl derivative by using $Rh_2(OAc)_4$ **36**.[778]

4.20.4.1.4.6 Vinylarenes

4.20.4.1.4.6.1 Indene

The reaction of indene **230** with some diazoacetic esters in the presence of the ferrocene-heterocyle-CuOTf catalyst **231** affords very high *trans*/*cis*-selectivities (R = Et, 98:2; Bu^t, 94:6; 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168**, 100:0), albeit with very low enantioselectivity (2–10% *ee*).[791]



(58)

An almost quantitative *cis*-preference (*cis*/*trans* > 99:1) and very high yield (98%) has been obtained in the reaction between **230** and ethyl diazoacetate **12** at 0 °C using a chiral rhodium catalyst in CH_2Cl_2.[752]

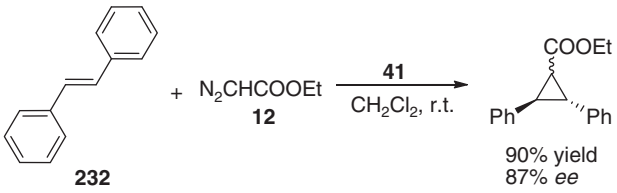
4.20.4.1.4.6.2 1,1-Diphenylethylene

The achiral version of the cyclopropanation reaction between 1,1-diphenylethylene **108** and ethyl diazoacetate **12** can be quantitatively achieved using readily available catalysts ($CuSO_4$ in benzene,[792] $Rh_2(OAc)_4$ **36** in CH_2Cl_2).[793] However, a great effort has been made in order to achieve the enantioselective version of the 1,1-diphenylethylene **108**+ethyl diazoacetate **12** reaction. For further details, see Section 4.20.4.1.5.2.

The reaction of 1,1-diphenylethylene **108** with 2-diazo-1-indanone **165** in the presence of $Rh_2(OAc)_4$ **36** leads to the corresponding cyclopropane in 69% yield.[124]

4.20.4.1.4.6.3 Stilbenes

Both (*E*)- (**232**) and (*Z*)-stilbenes (**233**) can be efficiently cyclopropanated with ethyl diazoacetate **12** using copper catalysts. Thus, $Cu(MeCN)_4(BF_4)_2$ **234** can be used as a catalyst in the **232** reaction (87% yield).[794] As an alternative, $CuSO_4$ **112** in benzene can also be used for the reactions of both stilbenes (*Z* isomer: 81%, *E* isomer: 77%, both yields calculated after saponification).[795] Compound **232** can be cyclopropanated with ethyl diazoacetate **12** with high enantioselectivity by using the chiral Cu-terpyridine complex **41** as a catalyst (90% yield, 87% *ee*).[349]



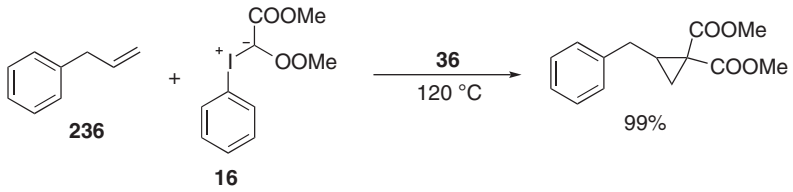
(59)

A special interest must be paid to the reactions of both stilbenes with methyl phenyldiazoacetate **39** as no significant yields can be obtained in the presence of $Rh_2(OAc)_4$ **36**.[150] Instead, the use of $AgSbF_6$ allowed obtaining good yields (*E*, 84% yield; *Z*, 54% yield). This later catalyst afforded 34% yield in the reaction of **232** with methyl styryldiazoacetate **235**.

4.20.4.1.4.6.4 Allylbenzene

A number of cyclopropanation reactions have been achieved by using allylbenzene **236** as a substrate. Thus, a high yield (99%) has been obtained in the reaction of **236** with the dimethyl malonate-derived phenyliodonium ylide **196** in the presence of $Rh_2(OAc)_4$ **36**.[771] However, a major drawback in typical cyclopropanation reactions of **236** involving nonsymmetric ketocarbenoids lies on the low stereoselectivities, such as that obtained with ethyl diazoacetate **12** in the presence of $Cu(OTf)_2$ in HFIP (*trans*/*cis* = 56:44, 56% yield).[488] A significant stereoselectivity increase can be obtained using a bulky diazoacetic ester. Thus, good *trans*/*cis* ratios and excellent enantioselectivities have been obtained for the **236**+2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168** by using some BR_2-bridged ^{t}Bu–bisoxazolines–Cu (R = Me, *trans*/*cis* = 93:7, 99% *ee trans*; R = 3,5-bis(trifluoromethyl)phenyl,

trans/*cis* = 92:8, 97% *ee*, 66% yield)[417] As an alternative method for obtaining high stereoselectivities, *tert*-butyl cyanodiazoacetate **205** in the presence of **130** (*trans*/*cis* > 99:1, 91% *ee*) can be used as a ketocarbenoid.[194]

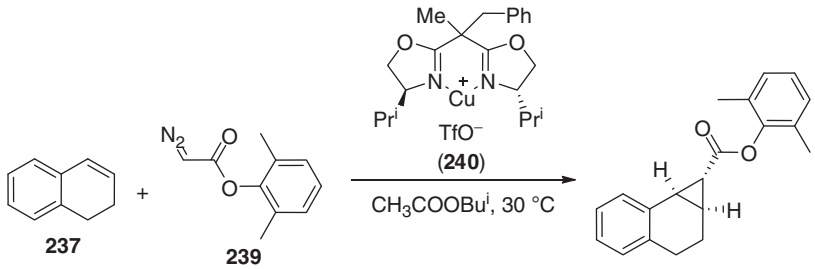


(60)

4.20.4.1.4.6.5 1,2-Dihydronaphthalene

1,2-Dihydronaphthalene **237** has been reacted with dimethyl diazomalonate **11** in the presence of $Rh_2(esp)_2$ **71** to afford the corresponding cyclopropane in 82% yield.[761] Both *exo* and *endo* cyclopropanes can be obtained from **237** and nonsymmetric diazocarbenoids. Thus, a 2.4:1 *exo*/*endo* ratio has been obtained from the reaction with ethyl diazoacetate **12** in the presence of Cu-exchanged phosphotungstic acid (80% yield).[293] However, most data on cyclopropanation reactions of 1,2-dihydronaphthalene are usually restricted to yields. Thus, 1,2-dihydronaphthalene has been reacted with ethyl diazoacetate **12** from a commercial source in the presence of a carborane phosphine–Rh complex (91% yield)[545] or obtained *in situ* in the presence of TPPRhI (**119**, 53% yield).[760]

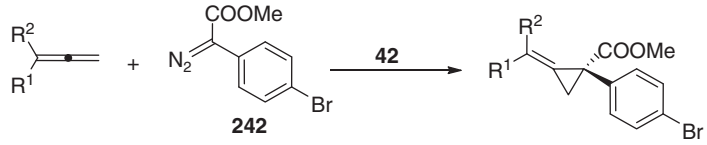
Other diazo compounds have also been used in cyclopropanation reactions with **237** by using different catalysts, such as methyl phenyldiazoacetate **39**–$AgSbF_6$ (80% yield), methyl styryldiazoacetate **235**–$AgSbF_6$ (57% yield),[150] methyl nitrodiazoacetate **238**–Rh_2(octanoate)$_4$ **83** (84% yield), and **238**–Rh_2(pivalate)$_4$ (72% yield).[202] 1,2-Dihydronaphthalene **237** reacts with 2,6-dimethylphenyl diazoacetate **239** by using the bisoxazoline–Cu complex **240** as a catalyst with very high yield (95%) and stereoselectivities (*trans*/*cis* = 97:3, 89% *ee trans*).[796]



(61)

4.20.4.1.4.7 Allenes

A number of allenes can be cyclopropanated with aryldiazoacetic esters with high enantioselectivities (80–90% *ee*) and yields (54–79%) by using Rh_2(*S*-DOSP)$_4$ **42**. The high yield found for the reaction of 3-(trimethylsilyl)buta-1,2-diene with methyl *p*-bromophenyldiazoacetate **242** in comparison with other 1,1-disubstituted allenes can be attributed to a donor effect of the silyl group.[797]

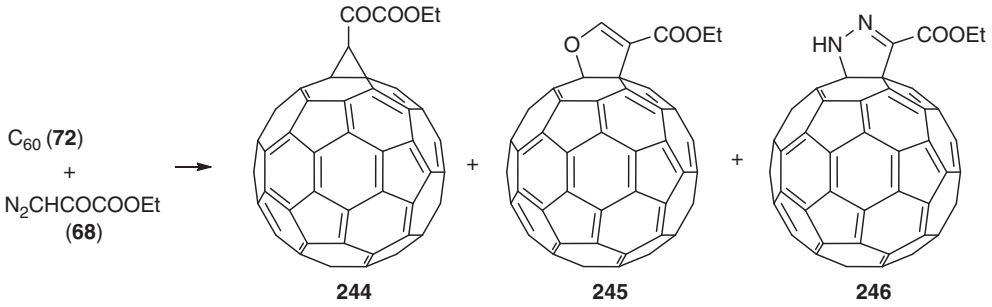


(62)

Ethyl 2-diazo-3-oxobutanoate reacts with some allenes[195,798,799] in the presence of $Rh_2(OAc)_4$ **36** to yield the corresponding alkylidenecyclopropanes.

4.20.4.1.4.8 Fullerenes

A review on [2+1] and [2+2] cycloaddition reactions of fullerenes has been published.[800] Furthermore, the chemistry of fullerenes with diazo compounds has also been reviewed.[801] Cyclopropanation reactions through pyrazolines have also been carried out using fullerenes. Thus, buckminsterfullerene **72** can be functionalized with ethyl diazopyruvate **68** in thermal conditions, leading to a mixture of C_{60} derivatives including cyclopropane **244**, dihydrofuran **245**, and 2-pyrazoline **246** (equation 63; **Tables 22** and **23**).[802]



(63)

Table 22 Results of the reaction between different substituted allenes and methyl *p*-bromophenyldiazoacetate catalyzed by **42**.[803] Reactions carried out in hexane at room temperature

R^1	R^2	*Yield (%)*	ee *(%)*
Ph	H	76	90
4-ClC_6H_4	H	61	84
C_5H_{11}	H	60	88
CH_2Ph	H	54	>80
Ph	CH_3	33	86
CH_3	CH_3	30	90
Me_3Si	CH_3	79	85

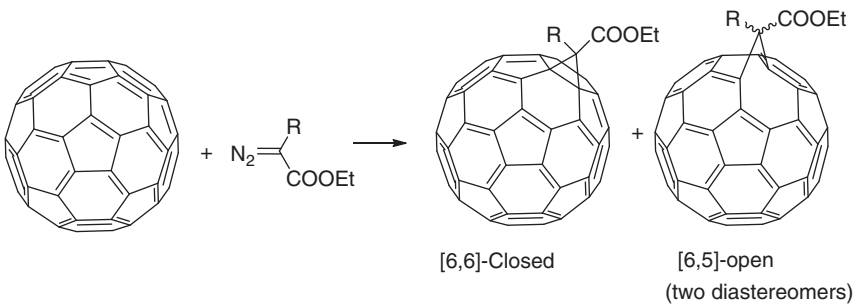
Table 23 Results (including **244**:**245**:**246** ratios) of the thermal reactions between **72** and **68** under different conditions[802]

Solvent	*Temperature (°C)*	*Time (h)*	*Yield (%)*	***244***	***245***	***246***
1-Methylnaphthalene	30	120	20	6	27	67
1-Methylnaphthalene	45	40	20	7	22	71
1-Methylnaphthalene	60	16	15	11	33	56
1-Methylnaphthalene	110	16	19	50	50	–
Toluene	50	72	13	–	–	100

The mechanism for the cyclopropanation reaction between **72** and ethyl diazoacetate **12** catalyzed by Pd was studied by Tuktarov et al.[76] The reaction of such species with C_{60} generates a palladacyclopropane, characterized by ^{31}P NMR. The palladacyclopropane can react with ethyl diazoacetate **12** to yield the corresponding palladacyclobutane (by N_2 extrusion). This palladacyclobutane can undergo a reductive elimination in the presence of PPh_3 to generate the corresponding cyclopropane (as well as the related isomer) (Scheme 27).

A number of diazoketones N_2CHCOR have been used in catalyzed cyclopropanation reactions for the functionalization of C_{60} **72** to afford the corresponding cyclopropanes with moderate yields (30–60%) (Table 24).[803]

Two types of reaction products are obtained in the reaction between **72** with ethyl diazoacetate **12** in the presence of **36**, named as [6,6]-closed methanofullerene (i.e., a cyclopropane) and [6,5]-open fulleroid. Although the reaction in thermal conditions (110 °C) led to a predominance of [6,5]-open products (86:14), the catalytic reaction in 1-methyl naphthalene at room temperature showed a clear preference for cyclopropanes (98:2) (Table 25).[455]



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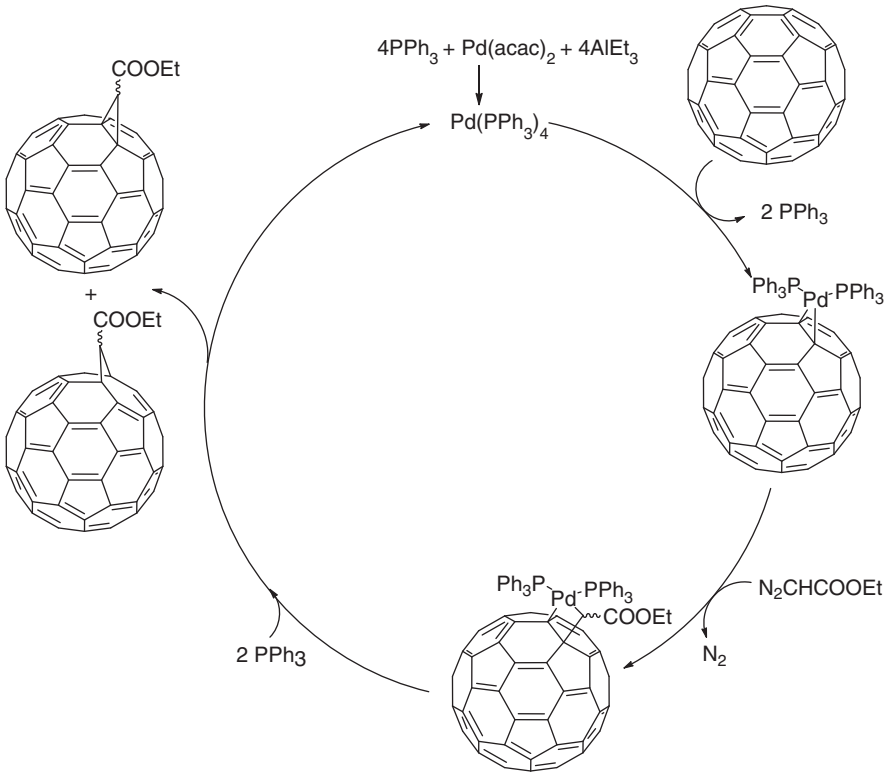


Scheme 27

Table 24 Yields of the reactions between C_{60} **72** and a number of diazoketones N_2CHCOR catalyzed by the catalytic system $Pd(acac)_2$-PPh_3-$AlEt_3$[803]

R	*Yield (%)*
Cyclopropyl	45
Cyclobutyl	45
Cyclopentyl	45
Adamant-1-yl	40
Furan-2-yl	30
Thiophen-2-yl	35
2-Pyridyl	58
2-Phenylquinolin-4-yl	60

Table 25 Yields of the reactions between C_{60} **72** and a number of diazoketones N_2CHCOR catalyzed by the catalytic system $Pd(acac)_2$–PPh_3–$AlEt_3$ (equation 64)[803]

R	*Catalyst*	*Solvent*	*Temperature (°C)*	*Yield (%)*	*[6,6]-Closed/[6,5]-open*	*References*
H	–	Toluene	110	35	17:83	804
H	36	Toluene	r.t.	21	87:13	455
H	36	1-Methylnaphthalene	r.t.	42	98:2	455
COOEt	–	Toluene	110	10	n.d.	804
COOEt	36	1-Methylnaphthalene	80	33	90:10	455

4.20.4.1.4.9 Other electron-rich alkenes

4.20.4.1.4.9.1 Vinyl ethers

A number of alkyl vinyl ethers have been used as substrates in cyclopropanation reactions. The *trans*-selectivity obtained in the $Rh_2(OAc)_4$ **36**-catalyzed reaction between ethyl vinyl ether **247** and a number of diazacetic esters $N_2CHCOOR$ is slightly

dependent on the alkyl group bulkiness (Et, 62%; 2,3,4-trimethylpentan-3-yl, 67%; 3-isopropyl-2-methylheptan-3-yl, 70%; 2,6-di-*tert*-butyl-4-methylphenyl, 71%).[135] The **247**+ethyl diazoacetate **12** reaction can be achieved in an enantioselective way by means of some Ru–salen catalysts. For example, catalyst **248** allows obtaining 80% yield, *trans*/*cis* = 80:20.[619]

4.20.4.1.4.9.2 Allyl ethers

Despite the high reactivity of allyl ethers toward diazo compounds, the yields obtained for cyclopropane products are often decreased by the competition of the carbene insertion reaction on the Cα–H bond (see Section 4.20.4.1.1.3). Thus, the reaction of allyl butyl ether **249** with methyl diazoacetate **54** catalyzed by $Rh_2(OAc)_4$ **36** in [bmim]BF_4 leads to cyclopropanes in 57% yield (*trans*/*cis* = 50:50) and 19% yield of the C–H insertion products.[805] Instead, the reaction of allyl ethyl ether **249** with ethyl diazoacetate **12** in the presence of $Tp^{Ms}Cu$ **251** leads to 59% cyclopropanation, 21% dimerization, and 20% 2,3-sigmatropic rearrangement.[365]

Cyclopropanation reactions of allylic substrates are sensitive to steric encumbrance. Thus, the use of methyl *p*-(bromophenyl) diazoacetate **242** in the presence of Rh_2(*S*-DOSP)$_4$ **42** with allyl acetate **252** affords cyclopropanes in 89% yield (78% *de*, 78% *ee*), whereas the corresponding reaction of allyl *tert*-butyldimethylsilyl ether **253** leads to cyclopropanes in 38% yield.[806]

High yields have been obtained in $Rh_2(esp)_2$ **71**-catalyzed cyclopropanation reactions of dimethyl diazomalonate **11** with a number of allyl ethers (Bu, 87%; Ph, 72%; and Bn, 83%).[761] For the sake of comparison, the use of the dimethyl malonate-phenyliodonium ylide **196** with allyl benzyl ether **254** in $Rh_2(esp)_2$ **71**-catalyzed reaction led to 69% yield.[264]

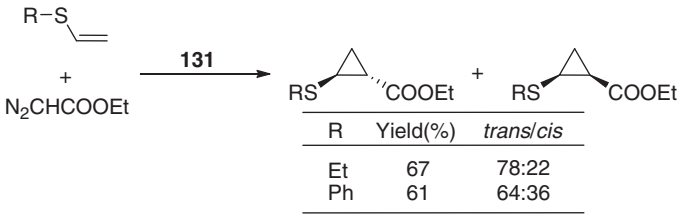
Isobutyl *O*-allyl lactate **255** can be cyclopropanated with *tert*-butyl diazoacetate **133** in the presence of $Rh_2(OAc)_4$ **36** in 78% yield.[807]

4.20.4.1.4.9.3 Silyl enol ethers

Silyl enol ethers derived from acetophenone, cyclopentanone, and cyclohexanone have been reacted with some diazoacetic esters in the presence of Cu–semicorrin, azasemicorrin, and bisoxazoline catalysts.[808] Interestingly, very slight variations on the *trans*/*cis* ratios and somewhat larger enantioselectivity changes are observed as a function of the diazoacetate alkyl group, whereas significant differences are found depending on the catalyst. See Section 4.20.4.1.5.2.1 for detailed results obtained with these substrates.

4.20.4.1.4.9.4 Vinyl thioethers

The reactions of ethyl and phenyl vinyl sulfides with ethyl diazoacetate **12** in the presence of (TPP)Ru(CO) **131** leads to cyclopropanes with modest yields and *trans*/*cis*-selectivities (equation 65).[604]

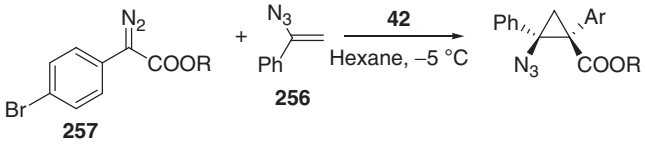


R	Yield(%)	*trans*/*cis*
Et	67	78:22
Ph	61	64:36

(65)

4.20.4.1.4.9.5 α-Azidostyrene

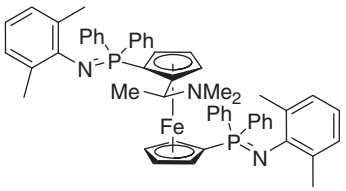
α-Azidostyrene **256** can be cyclopropanated with aryldiazoacetic esters using chiral rhodium catalysts with high diastereo- and enantioselectivities.[809] Thus, the reaction between **256** and *p*-bromobenzyl phenyldiazoacetate **257** in the presence of Rh_2(*S*-DOSP)$_4$ **42** was achieved with 92% yield, high *cis*-selectivity (*cis*/*trans* = 99:1), and 95% *ee*, i.e., 89% total yield in a single cyclopropane stereoisomer.



(66)

4.20.4.1.4.9.6 Silylalkenes

Triethylvinylsilane **258** reacts with ethyl diazoacetate **12** in the presence of $Ru(DMSO)_4Cl_2$ and **259** to afford the corresponding cyclopropanes (90% yield, *trans*/*cis* = 91:9, 98% *ee trans*, and 99% *ee cis*).[628] Compound **258** reacts with several diazoacetatetic esters (Et, Bu^t, 2,6-di-*tert*-butyl-4-methylphenyl) in the presence of CuOTf/**260** to afford the corresponding cyclopropanes with good yields (83–87%) and almost quantitative (from 99:1 to 100:0) *trans*/*cis*-selectivities albeit with very low enantioselectivities.[791]



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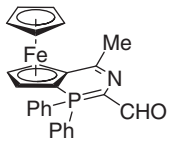
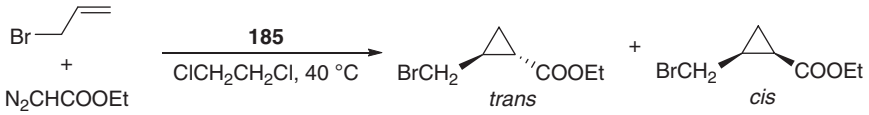


260

Trimethylsilyl ketene dimethylketal **261** reacts with ethyl diazoacetate **12** in the presence of $Cu(acac)_2$ **110** to afford the corresponding cyclopropane in 72% yield.[810]

4.20.4.1.4.9.7 Allyl bromide

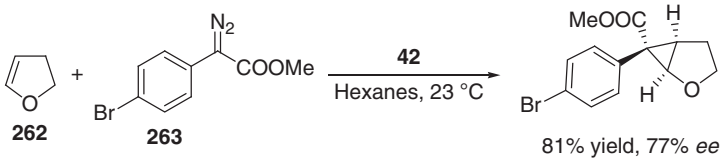
Allyl bromide was reacted with ethyl diazoacetate **12** in the presence of a Schiff base–Cu complex **185** (*trans*/*cis* = 71/29).[311]



(67)

4.20.4.1.4.9.8 2,3-Dihydrofuran

2,3-Dihydrofuran **262** was reacted with ethyl *p*-bromophenyldiazoacetate **263** in the presence of $Rh_2(S\text{-DOSP})_4$ **42** to provide the corresponding cyclopropane in 81% yield (equation 68).[515]

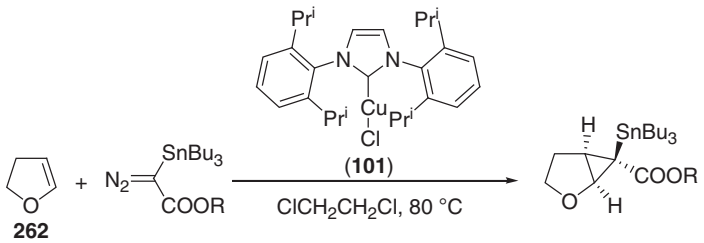


(68)

Reaction of **262** with phenyldiazoacetic esters leads to good yield of the cyclopropane products, irrespective of the activation procedure. Thus, the thermal, noncatalyzed reaction of the methyl ester **39** leads to 71% yield (>95:5 *dr*).[51] When catalyzed by a trisoxazoline–copper complex, the reaction of the ethyl ester **263** yields 80% (83% *ee*).[152]

Reaction with methyl 2-diazo-3-(3-methylindol-1yl)-3-oxopropanoate **188** under $Rh_2(esp)_2$ **71** catalysis afforded 75% yield.[181]

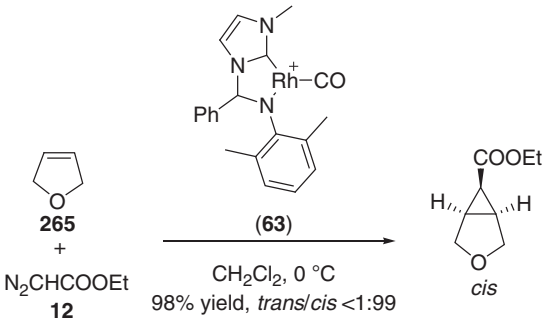
Compound **262** reacts with tributylstannyldiazoacetate esters in the presence of a Cu–NHC carbene **101** as a catalyst (Et, 56% yield; Bu^t, 58% yield) with high stereoselectivities (both *dr* ≥95:5) (equation 69).[232]



(69)

4.20.4.1.4.9.9 2,5-Dihydrofuran

Cyclopropanation of 2,5-dihydrofuran **265** with ethyl diazoacetate **12** by using $Rh_2(OAc)_4$ **36** as a catalyst has been used in the synthesis of some antiviral agents in two patents (50% yield).[811,812] Instead, excellent results were obtained for the same reaction by using **63** as a catalyst (98% yield, *trans*/*cis* <1:99) (equation 70).[752]



(70)

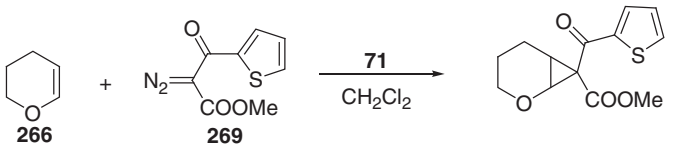
4.20.4.1.4.9.10 3,4-Dihydro-2*H*-pyran

3,4-Dihydro-2*H*-pyran **266** can react with nonsymmetric ketocarbenoids to generate two diastereomers (named as *endo* and *exo*). Interestingly, the treatment of **266** with ethyl diazoacetate **12** at high temperature in the presence of $CuSO_4$ **112** afforded a single diastereomer (62% yield).[813] Nevertheless, an *exo* preference is usually found in the reactions between **266** and ethyl diazoacetate **12** in the presence of a number of catalysts, such as $Cu(OTf)_2$ in HFIP (55% yield, *exo*/*endo* = 54:46),[488] $Rh_2(O_2PMe_2)_4$ (80% yield, *exo*/*endo* = 5.6),[765] and $Cu_3(BTC)_2$ (90% yield, 91% *dr*).[151]

The diastereoselectivity of the reactions of **266** with diazoacetic esters can be increased by using encumbering alkyl groups. Thus, the reaction of *tert*-butyl diazoacetate **133** in the presence of CuOTf **78** and a concave ligand provided good stereoselectivities (no ligand: *exo*/*endo* = 73:27, 77% yield; **197**: *exo*/*endo* = 81:19, 80% yield; **199**: *exo*/*endo* = 80:20, 94% yield).[814] Higher selectivities were obtained in the presence of $Rh_2(OAc)_4$ **36** by using some hindered diazoacetates (2,6-di-*tert*-butyl-4-methylphenyl, *exo*/*endo* = 97:3, 92% yield; 3-isopropyl-2-methylheptan-3-yl, *exo*/*endo* = 85:15, 88% yield).[135]

Exo cyclopropanes were obtained in the reactions between **266** and some alkyldiazoacetic esters. Thus, the reactions of methyl 2-diazobutanoate **267** under $Rh_2(tpa)_4$ **162** catalysis (57% yield)[495] or $Rh_2(S\text{-DOSP})_4$ **42** (57% yield, 87% *ee*)[815] and methyl 2-azobut-3-enoate **268** under $Rh_2(octanoate)_4$ **83** catalysis 56% yield[816] provided essentially pure *exo* diastereomeric cyclopropanes.

Dihydropyran **266** has also been reacted with other ketocarbenoids with high stereoselectivities, such as methyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate **269** in the presence of $Rh_2(esp)_2$ **71** (66% yield)[179] or tributylstannyldiazoacetatic esters (Et, 63% yield; Bu^t, 62% yield) catalyzed by Cu(I)NHC **101** (*endo*/*exo* > 95:5).[232]



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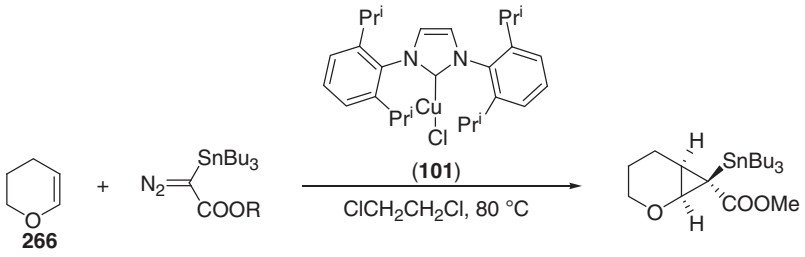
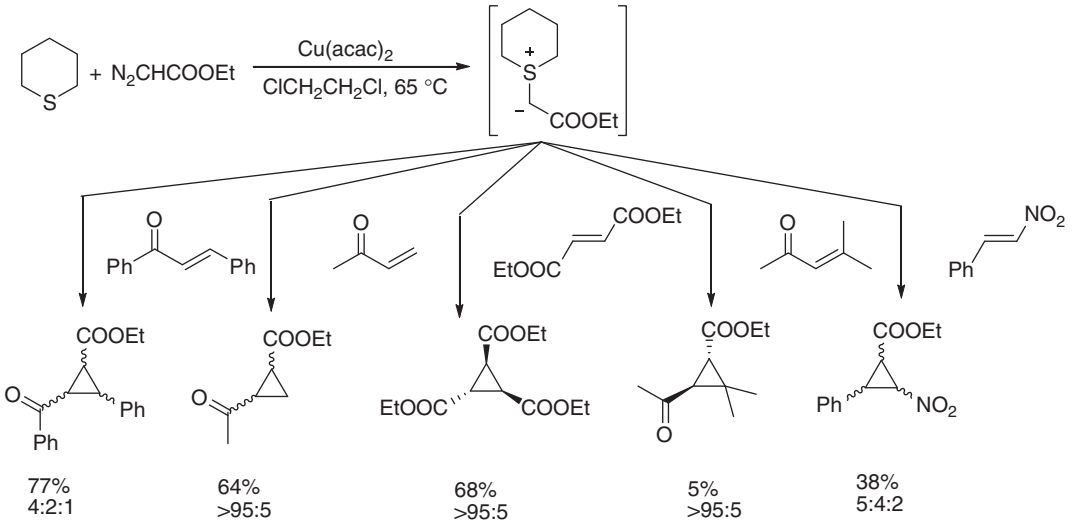


(72)

4.20.4.1.4.10 Electron-poor alkenes

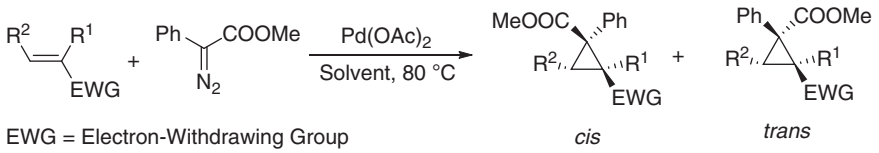
Electron-deficient olefins are typically inert in typical cyclopropanation reaction conditions with diazo compounds in the presence of Rh or Cu derivatives,[173] presumably due to the predominance of other competing reactions, such as carbene dimerization. To avoid such a handicap, a number of alternative methods for the addition of ketocarbenoids to electron-poor alkenes have been developed.

A possible technique to minimize the carbene dimerization consists on the use of *in situ*-generated ylides from the diazo compound in the presence of a catalyst. Thus, chalcone **270**, butenone **271**, diethyl fumarate **272**, mesityl oxide **273**, and *β*-nitrostyrene **274** can be cyclopropanated by using ethyl diazoacetate **12** in the presence of $Cu(acac)_2$ **110** and thiane (**Scheme 28**).[817]



Scheme 28

Palladium catalysts can be used for cyclopropanation of electron-poor alkenes with diazocompounds. Thus, $Pd(OAc)_2$ **275** has proven to be an efficient catalyst for the reactions of a number of electron-deficient olefins with methyl phenyldiazoacetate **39** with good yields and high *cis*/*trans*-stereoselectivities (equation 73; Table 26).[173]



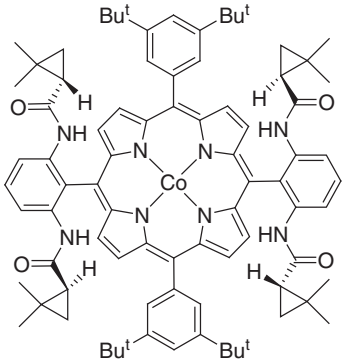
(73)

Table 26 Results of the reactions of $Pd(OAc)_2$-catalyzed reactions between different electron-deficient olefins and methyl phenyldiazoacetate **39** (equation 73)

R^1	R^2	*EWG*	*Solvent*	*Additive*	*Yield (%)*	trans/cis
H	H	COOMe	PhMe	–	86	<5:95
H	H	COOBu	PhMe	–	79	<5:95
Me	H	COOMe	PhMe	–	63	<5:95
H	Ph	COOMe	PhMe	1,1′-Bis(diphenylphosphino)ferrocene	30	11:89
H	H	CHO	PhMe	1,1′-Bis(diphenylphosphino)ferrocene	15	<5:95
H	H	$CONEt_2$	PhMe	1,10-Phenanthrolin	58	50:50
H	H	CN	PhCl	1,10-Phenanthrolin	73	50:50

Abbreviation: EWG, electron-withdrawing group.

The Co catalyst **130** has proven to yield excellent yields, diastereo- and enantioselectivities with a number of diazo esters and a number electron-deficient alkenes (including α,β-unsatured ketones, esters, and amides, as well as diethyl maleate **276**).[663] For more details concerning the enantioselective versions of these reactions, see Section 4.20.4.1.5.2.

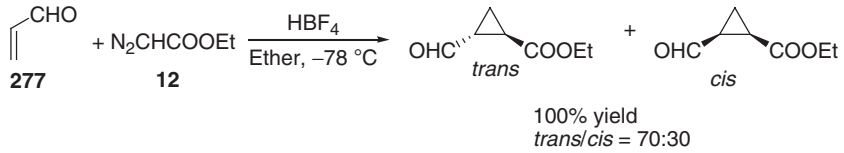


130

Nevertheless, many electron-poor olefins are usually cyclopropanated in reactions with ylides through zwitterions.

4.20.4.1.4.10.1 Acrolein

Acrolein **277** can be quantitatively cyclopropanated with ethyl diazoacetate **12** at −78 °C in the presence of HBF_4 in ether (*trans*/*cis* = 70:30) (equation 74).[68] Interestingly, no cyclopropane product was obtained when the same reaction was carried out in CH_2Cl_2 at 0 °C.

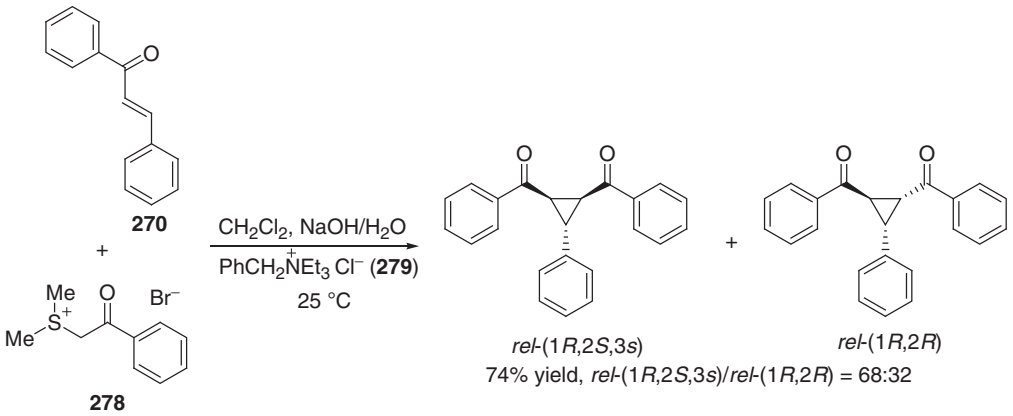


(74)

4.20.4.1.4.10.2 Chalcone

Chalcone **270** reacts with ethyl diazoacetate **12** in the presence of thiane and $Cu(acac)_2$ **110** to afford 77% yield (isomeric ratio = 4.2:1).[817]

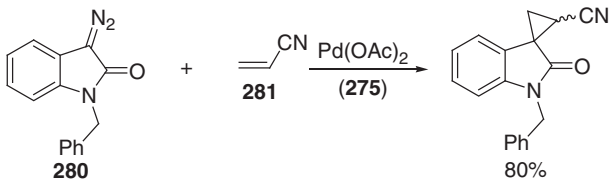
Substituted chalcones can be cyclopropanated with *in situ*-prepared substituted phenacyl-sulfonium ylides under phase–transfer catalysis. For example, the treatment of parent chalcone with dimethylphenacylsulfonium bromide **278** and CH_2Cl_2 with aqueous NaOH and triethylbenzylammonium chloride **279** led to 74% yield (*rel*-(1*R*,2*S*,3*s*)/*rel*-(1*R*,2*R*) = 68:32).[251]



(75)

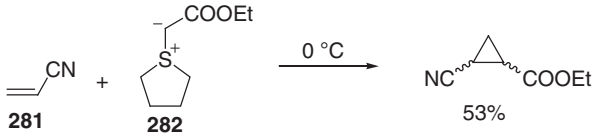
4.20.4.1.4.10.3 Acrylonitrile

1-Benzyl-3-diazoindolin-2-one **280** reacts with acrylonitrile **281** in the presence of $Pd(OAc)_2$ **275** to afford the corresponding cyclopropane as a mixture of two diastereomers in 80% yield.[818]



(76)

Sulfonium ylides can be also used in cyclopropanation reactions of **281**. Thus, **281** was reacted with the ethyl acetate tetrahydrothiophenium ylide **282** at 0 °C leading to 53% yield.[819]



(77)

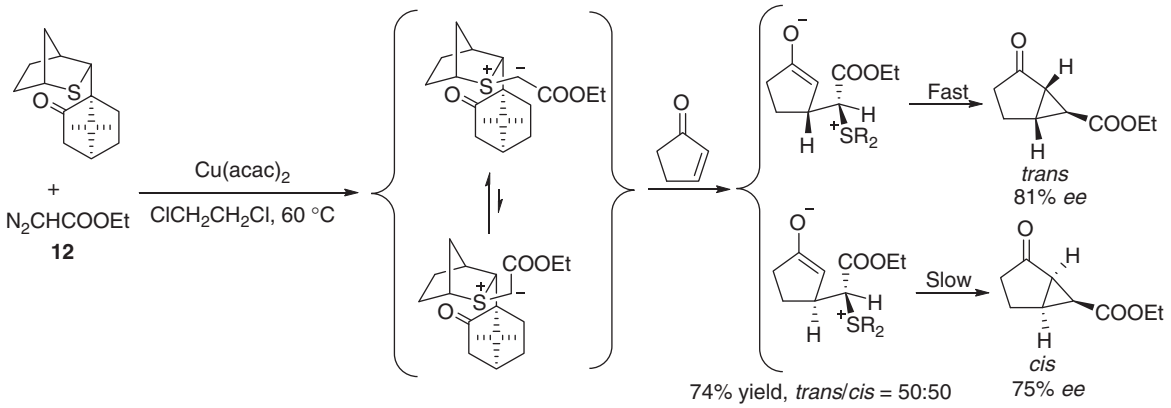
4.20.4.1.4.10.4 Arylcyanoacrylic esters

A number of arylcyanoacrylic esters have been cyclopropanated using a phenacylarsonium ylide in good yields (62–94%).[820]

4.20.4.1.4.10.5 Other α,β-unsaturated nitriles

A number of substituted benzylidenemalonitriles have reacted with phenacylarsonium ylides to yield the corresponding cyclopropanes with good yields (80–90%).[248]

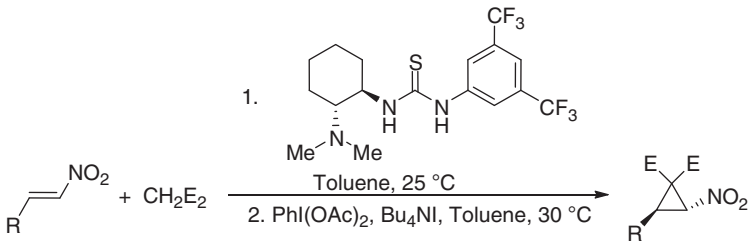
Cyclopentenone **283** reacts with ethyl diazoacetate **12** in the presence of $Cu(acac)_2$ **110** and a chiral sulfide to afford an *endo*/*exo* (1:1) mixture of cyclopropanes with high enantioselectivities (81% *ee exo*, 75% *ee endo*) (Scheme 29).[285]



Scheme 29

4.20.4.1.4.10.6 Nitroalkenes

A number of substituted nitroethylenes can undergo cyclopropanation reactions by using phenyliodonium ylides obtained *in situ* from several dicarbonylcarbenene precursors in the presence of a chiral organocatalyst with good yields and high enantio- and diastereoselectivities (equation 78; Table 27).[821]



(78)

Table 27 Results of the reactions between different nitroalkenes and some iodonium ylides in the presence of a chiral organocatalyst (equation 78)

R	*E*	*Yield (%)*	*% ee*	dr
Ph	COOEt	73	87	>95:5
4-MeO-C_6H_5	COOEt	52	89	>95:5
4-Cl-C_6H_5	COOEt	87	90	>95:5
4-F-C_6H_5	COOEt	71	93	>95:5
2-Br-C_6H_5	COOEt	81	94	>95:5
1-Naphthyl	COOEt	80	93	>95:5
2-Thiophenyl	COOEt	35	89	>95:5
Ph	COOMe	81	92	>95:5
Ph	COMe	60	86	>95:5

Sulfonium ylides can also be used in cyclopropanation reactions of nitroalkenes. Thus, the methyl acetate dimethylsulfonium ylide reacts with nitromethylydenecyclohexane (68% yield) and with 2-methyl-1-nitropropene (65% yield).[822]

4.20.4.1.5 Asymmetric reactions

4.20.4.1.5.1 Chiral auxiliaries

Selective formation of setereogenic centers in intermolecular ketocarbene additions to alkenes can be induced through the use of chiral auxiliaries either on the carbene precursor or on the olefin. Of course, it is easier to link the chiral auxiliary to the carbonyl carbene precursors, usually as an ester of a chiral alcohol; many more examples have been described using the first strategy. Most of the papers dealing with chiral auxiliaries were published in the 1990s. However, the early and impressive development of chiral catalysts for these reactions (which will be revised in Section 4.20.4.1.5.2) resulted in the almost complete neglect of that strategy.

4.20.4.1.5.1.1 Chiral auxiliary on the carbene precursor

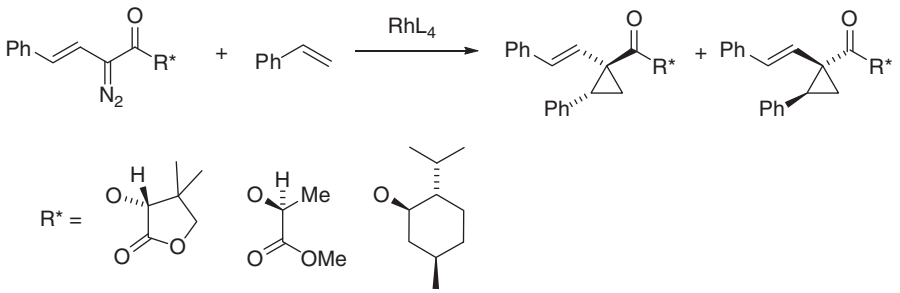
First of all, a caveat must be opened here concerning the use of diazoesters of chiral alcohols in metal-catalyzed cyclopropanation reactions. Although there are many references describing the use, for instance, of menthyl diazoacetate, **144**(either from (−)-**284** or (+)-**284**), in combination with chiral catalysts, most of the asymmetric induction in these cases comes from the combination of the chiral catalyst with a bulky ester, as demonstrated by the good results obtained with other bulky, nonchiral alcohols, like 2,6-di-*tert*-butyl-4-methylphenol **285**, and the scarce double asymmetric induction effect observed when both enantiomers of the chiral auxiliary are compared. For further details on these cases dealing with chiral catalysis, see Section 4.20.4.1.5.2. In this section, only those examples where the chiral auxiliary is the only source of enantioselection for the reaction will be considered.

One of the first works describing the use of chiral auxiliaries in metal-catalyzed cyclopropanation reactions was published by Davies and Cantrell, who described the use of several chiral vinyl diazoesters, based on common, inexpensive chiral alcohols, such as (1*R*,2*S*,5*R*)-menthol ((−)-**284**), (*S*)-methyl lactate (**286**), and (*R*)-pantolactone (**287**), among others.[490,823]

The best results were obtained using **287** as the chiral auxiliary, leading up to 91% yield with 89% *de* (approximately 17 of diastereomeric ratio) in the cyclopropanation of styrene catalyzed by $Rh_2(OAc)_4$ **36** at 0 °C. This results could be subsequently improved by using $Rh_2(oct)_4$ **83** as the catalyst (84% yield with 97% *de*, or approximately 66 *dr*).[490] With these conditions, other alkenes also led to good asymmetric inductions results (Table 28).

Table 28 Results obtained in the cyclopropanation of alkenes with the (*E*)-2-diazo-4-phenylbut-3-enoate of (*R*)-pantolactone (equation 79)

R^1	de *(%)*	*Yield (%)*
Ph	97	84
4-ClC_6H_4	>95	92
4-$MeOC_6H_4$	>95	75
EtO	92	71
OCH_2CH_2	66	86
$OCH_2CH_2CH_2$	47	65
AcO	90	42



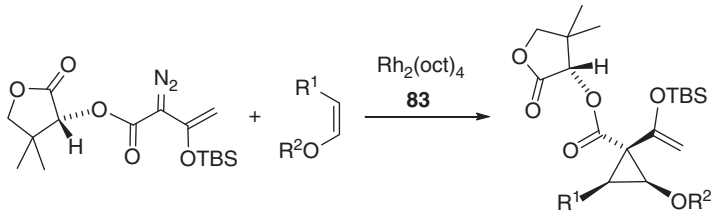
(79)

Poorer results are obtained when the chiral alcohol is attached as a diazoacetate ester. **284**, **287**, or 2-Phenylcyclohexanol **288** are hardly able to provide asymmetric inductions better than 30% *de* (approximately 2:1 diastereomeric ratio) in the cyclopropanation of styrene catalyzed by **36**.[140]

Davies and coworkers have also described the efficient use of chiral esters of vinyl carbene precursors in cyclopropanation reactions catalyzed by **83**.[509,824] Once again, the best asymmetric induction results are obtained with **287** (Table 29).

Oppolzer's sultam **289** has also been employed to prepare a sultam carbenoid, which was used in cyclopropanation reactions catalyzed by **36**,[172] or by metal–porphyrin complexes (Table 30).[171]

Table 29 Results obtained in the cyclopropanation of vinyl ethers with (*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-diazobut-3-enoate

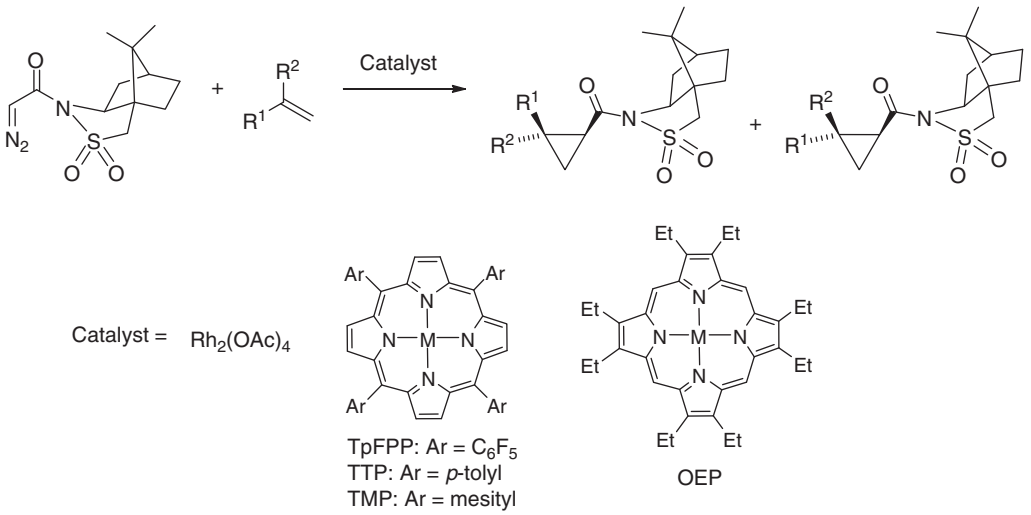


R^1	R^2	de *(%)*	*Yield (%)*
H	Bu	71	76
Me	Et	n.d.	76
CH_2CH_2		68	94
Ph	Me	71	79
4-ClC_6H_4	Me	80	73

Table 30 Results obtained in the cyclopropanation of alkenes with the diazoacetamide of the Oppolzer's sultam (equation 80)

Catalyst	R^1	R^2	trans:cis	de trans *(%)*	de cis *(%)*	*Yield (%)*
$Rh_2(OAc)_4$ **83**	Bu^t	H	76:24	81	>98	85
$Rh_2(OAc)_4$ **83**	Me	Me	–	90		83
$Rh_2(OAc)_4$ **83**	Ph	H	68:32	67	70	67
TPP-Rh	Ph	H	41:59	28	74	5
TMP-Rh	Ph	H	33:67	82[a]	30[a]	11
TpFPP-Fe	Ph	H	73:27	63	65	33
OEP-Ru	Ph	H	96:4	54	84	60
TTP-Ru	Ph	H	94:6	57	99	60
TMP-Ru	Ph	H	74:26	80[a]	50[a]	50
OEP-Os	Ph	H	76:24	47	77	10
TTP-Os	Ph	H	79:21	35	65	30
TMP-Os	Ph	H	69:31	54[a]	29[a]	5

[a]The absolute configurations of the major *trans*- and *cis*-isomers are (*R*,*R*) and (*R*,*S*), respectively, opposites to those obtained with the rest of catalysts.
Abbreviations: OEP, octaethylporphyrin; TMP, tetramesitylporphyrin; TpFPP, tetrakis(pentafluorophenyl)-porphyrin; TPP, tetraphenylporphyrin; TTP, tristetraprolin.



(80)

Chiral ammonium enolates have also been used in asymmetric cyclopropanation reactions.[242] Thus, moderate to good enantioselectivities have been found in systems showing a strong preference for the attack of the alkene to a face of the ammonium

ylide because of the occurrence of a highly discriminating geometric feature (shielding by 8-phenylmenthyl substituent,[825–827] steric effect of a hydrocarboned tether,[828] cation–π interaction) (Tables 31–33; Schemes 30 and 31).[829]

Table 31 Results of the reactions between 8-phenylmethyl pyridinium-acetate and different alkylidenemalonitriles (equation 31)[825]

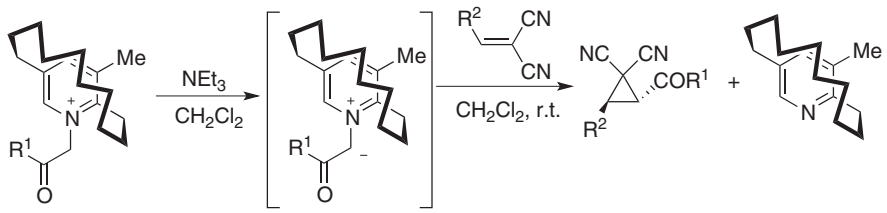
R	*Yield (%)*	*1R/1S*
Ph	78	83:17
4-$NO_2C_6H_4$	91	84:16
4-Pyridyl	82	84:16
Bu	97	70:30
Bu^i	96	73:27
Bu^t	99	86:14

Table 32 Results of the reactions between several acyl derivatives of 3-Methyl[10](2,5)parapyridinophane and alkylidenemalonitriles (Scheme 30)[828]

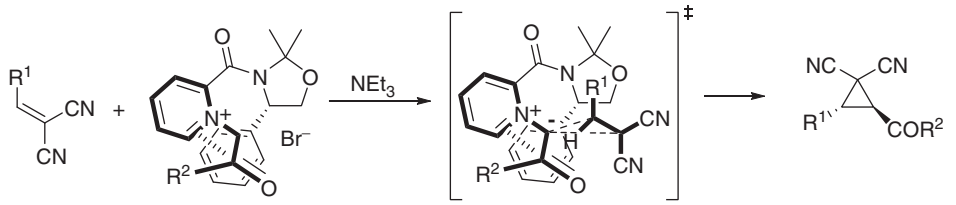
R^1	R^2	*Yield (%)*	ee *(%)*
Ph	Ph	98	50
Ph	Bu^t	74	98
Ome	Ph	86	62
OBu^t	Ph	98	94
OBu^t	2-Furyl	86	73
OBu^t	2-Thienyl	88	90
OBu^t	4-Cl-C_6H_4	64	94
OBu^t	4-MeO-C_6H_4	90	92
OBu^t	4-F-C_6H_4	81	96
OBu^t	4-Cl-C_6H_4	92	98
OBu^t	4-MeO-C_6H_4	62	96
OBu^t	4-Me-C_6H_4	87	99

Table 33 Results of the reactions between a set of 2-oxoalkylpyridinium derivatives with different alkylidenemalonitriles (Scheme 31)[829]

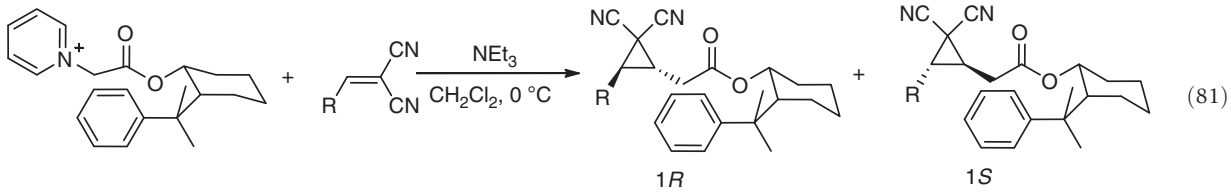
R^1	R^2	*Solvent*	*Yield (%)*	*% ee*
Ph	COOEt	CH_2Cl_2	78	66
Pyridyl	COOEt	CH_2Cl_2	80	68
1-Naphthyl	COOEt	CH_2Cl_2	81	78
Bu^t	COOBn	CH_2Cl_2	49	92
Bu^t	COPh	CH_2Cl_2	82	82
Cyclohexyl	COPh	CH_2Cl_2	89	82
Et	COPh	CH_2Cl_2	90	28



Scheme 30



Scheme 31

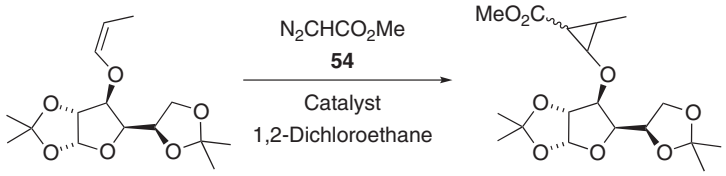


(81)

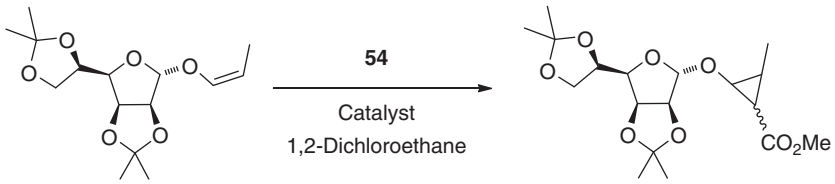
4.20.4.1.5.1.2 Chiral auxiliary on the alkene

Very few examples are known of chiral auxiliaries bound to the alkene in ketocarbene addition reactions. Schumacher and Reissig used chiral carbohydrate-derived enol ethers as substrates in the cyclopropanation with methyl diazoacetate **54**, catalyzed by copper and rhodium derivatives,[830] although the results were rather modest (**Table 34**).

Table 34 Results obtained in the cyclopropanation of carbohydrate-derived enol ethers with methyl diazoacetate **54**



Catalyst	*Conditions*	trans:cis	de trans *(%)*	de cis *(%)*	*Yield (%)*
$Cu(acac)_2$ **110**	50 °C/5 h	83:17	5	>95	54
$Rh_2(OAc)_4$ **36**	20 °C/24 h	79:21	4	>95	27



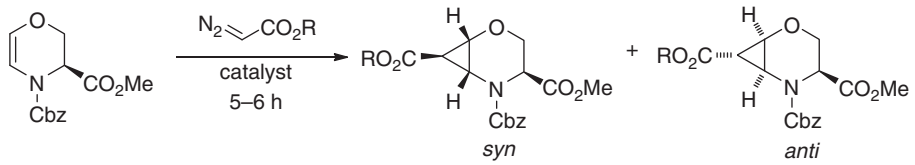
$Cu(acac)_2$ **110**	70 °C/24 h	79:21	6	43	67

Trabocchi and coworkers employed serine- and threonine-derived oxazines as substrates in the cyclopropanation with **54** and *tert*-butyl diazoacetate **133**, catalyzed by copper and rhodium derivatives, also with poor results when the catalyst was nonchiral (**Table 35**).[831]

4.20.4.1.5.2 Chiral catalysts

The enantioselective formation of cyclopropanes involving the intermolecular reaction of alkenes with chiral metal-carbene intermediates has become one of the preferred synthetic methods to obtain this kind of organic compounds. Furthermore, it has been a literal explosion in the literature, from the 1990s to date, describing new chiral catalysts using different metals and chiral ligands. However, the first example of enantioselective cyclopropanation reaction catalyzed by a chiral–metal complex in solution (the first example of enantioselective homogeneous catalysis, indeed) was described as soon as 1966 by Nozaki and coworkers.[297] Although the enantioselectivity was really modest (6% *ee*), this achievement represented a real breakthrough, which started a whole new field in asymmetric organic synthesis.

Table 35 Results obtained in the cyclopropanation of a serine-derived oxazine with methyl **54** and *tert*-butyl diazoacetate **133**

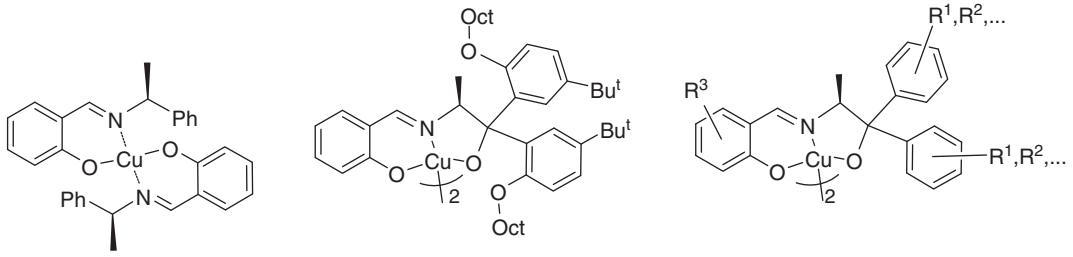


Catalyst	*R*	*Diazoester equivalent*	syn:anti	*Combined yield (%)*
$Rh_2(OAc)_4$ **36**	Et	3	62:38	72
$Cu(OTf)_2/PhNHNH_2$	Et	4.5	60:40	86
$Cu(OTf)_2/PhNHNH_2$	Bu^t	4.5	68:32	72

Although there are many possible ways to classify chiral catalysts, here it will be done by considering the metal to which the carbonylcarbenoid is linked. In many aspects, the metal determines not only the reaction but also the kind of chiral ligand employed. Given the synthetically useful orientation of this chapter, those catalysts leading to enantioselectivities higher than 80% *ee* (i.e., 90:10 enantiomeric ratio) will only be included. In the literature, there is a plethora of chiral catalysts tested in these kinds of reactions, but displaying only modest results.

4.20.4.1.5.2.1 Copper catalysts

Nozaki's catalyst **290** was a chiral salicylaldimine-copper complex, where the chirality was provided by the α-methylbenzylamine moiety used to prepare the imine. The next improvement was achieved with the ligand design carried out by Aratani, who employed chiral amino alcohols derived from amino acids, to prepare tridentate ligands. The corresponding copper complexes showed to be very efficient for the enantioselective cyclopropanation of 2,5-dimethyl-2,4-hexadiene **50** with (1*R*,2*S*,5*R*)-menthyl diazoacetate (1*R*,2*S*,5*R*)-**144** (94% *ee* in *trans*-cyclopropanes with 7/93 *cis*/*trans*-selectivity). This catalytic procedure was used in the industrial synthesis of chrysantemic acid derivatives.



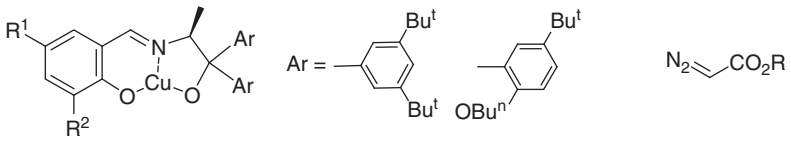
Nozaki's catalyst **290**

Aratani's catalysts

After the success of Aratani's catalysts, many variants have been proposed, by changing the substituents in the aromatic rings of the amino alcohol moiety,[310,317,318] by introducing substituents on the salicylaldehyde moiety,[131,311,312,317,318] by introducing a second stereogenic center in the amino alcohol moiety,[314,315] and even by doubling the imine substituent leading to binuclear copper catalysts.[310] The use of different diazoacetate esters to improve the stereoselectivities has also been considered.[311,317,318] Most of these catalysts have been tested in the benchmark cyclopropanation reactions of styrene **10** with alkyl diazoacetates, which will be extensively reviewed in Section 4.20.4.1.4.1. In general, the enantioselectivities in these reactions are moderate (approximately 80% *ee* in the best cases). Li and coworkers described that the introduction of a nitro group in the 5-position of the salicylaldehyde moiety leads to an improvement of the enantioselectivities, both in *trans*- and *cis*-cyclopropanes, although it does not affect the diastereoselectivity, which is rather low when ethyl diazoacetate **12** is used as the diazo compound.[131] Both stereoselectivities can be further improved by using bulkier diazoacetates, such as *tert*-butyl diazoacetate **133** and (1*R*,2*S*,5*R*)-**144** (up to 25:75 *cis*/*trans*-selectivity and >95% *ee*).[311] However, the results are much worse for other alkenes, such as 1-octene **28**, 2-methyl-1-pentene **291** or vinyl acetate **52**, and only the closely related 1,1-diphenylethene **108** leads to good enantioselectivities with these catalysts (**Table 36**).[311,315]

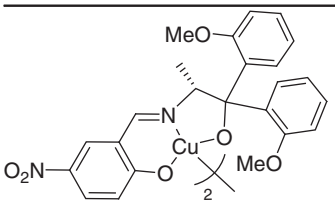
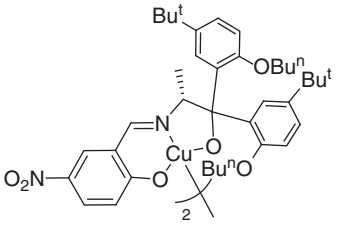
Itagaki and coworkers have revisited the enantioselective synthesis of chrisanthemic acid derivatives with Li's and other analogous catalyst. One of the main problems found is the low yield obtained in this transformation, below 30% for the catalysts displaying the best enantioselectivity. These results could be improved by using a Lewis acid in catalytic amounts (1:1 with the copper complex). With this modification yields increase to almost quantitative values, keeping the same diastereoselectivity and enantioselectivities, which are more than 90% *ee* in the major *trans*-cyclopropanes in the best cases (**Table 37**).[317,318]

Table 36 Results obtained in the cyclopropanation of styrene with alkyl diazoacetates, catalyzed by chiral salicyldimine–copper complexes



R^1	R^2	Ar	R	trans:cis	ee trans *(%)*	ee cis *(%)*
NO_2	H	3,5-Di-*tert*-butylphenyl	Me	48:52	82	89
NO_2	H		Et	53:47	84	93
NO_2	H		Bu^n	52:48	78	89
NO_2	H		Bu^i	55:45	86	98
NO_2	H		Bu^t	62:28	–	–
NO_2	H		l-Menthyl	76:24	98	95
Cl	H	2-*n*-Butoxy-5-*tert*-butylphenyl	Et	62:38	68	80
Cl	H		Bu^i	69:31	69	>98
Cl	Cl		Et	50:41	77	90
Cl	Cl		Bu^i	68:32	71	90
NO_2	H		Et	53:47	83	89
NO_2	H		Bu^i	66:34	74	>98
NO_2	NO_2		Et	56:44	69	81
NO_2	NO_2		Bu^i	66:34	61	79

Table 37 Results obtained in the cyclopropanation of **50** with **133**, catalyzed by chiral salicyldimine–copper complexes at room temperature

Catalyst	*Lewis acid*	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
	None	78:22	91	63	27
	$Al(OEt)_3$	78:22	91	62	90
	None	77:23	93	23	11
	$Al(OEt)_3$	77:23	93	24	86

The next breakthrough in the development of chiral copper catalysts for cyclopropanation reactions was achieved by the use of chiral C_2-symmetric semicorrin[382,384] and aza-semicorrin[385] ligands, described by Pfaltz and coworkers. Similar to salicylaldimines, semicorrins are also able to form neutral Cu(I) complexes by deprotonation of the NH bond, but the C_2-symmetry leads to an important improvement of the enantioselectivity of many cyclopropanation reactions. In the case of aza-semicorrins, they form cationic Cu(I) complexes, due to the *N*-methylation of the bridging nitrogen, but otherwise their behavior in cyclopropanation reactions is quite similar. In fact, semicorrins themselves were not much exploited from a practical point of view, due to synthetic limitations, for instance, the difficulty of modifying the nature of the substituents at the stereogenic centers, but they opened the door to new families of structurally similar ligands, which are able to form C_2-symmetric chelate complexes with copper, as are bisoxazolines and analogs.

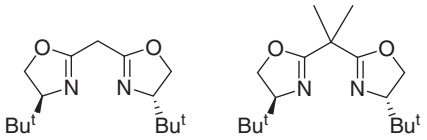
Chiral bisoxazoline ligands were almost simultaneously described by Masamune and Evans, just at the beginning of 1990s.[74,142,410] They present the advantage of the easy modification of the substituents, given that the stereogenic centers come from chiral amino alcohols, which are relatively easy to obtain in enantiomerically pure form. The synthetic schemes to obtain

these kinds of ligands are rather simple, and even one-pot procedures have been described.[832] As a consequence, some of them have become commercially available, and their use in different asymmetric catalysis applications has increased accordingly.

One of the first applications was namely the cyclopropanation reaction of alkenes with diazoesters, catalyzed by copper complexes, and very good results were obtained from the beginning in the benchmark reaction of styrene with diazoesters. Thus, Masamune and coworkers described 90% *ee* in *trans*-cyclopropanes when using ethyl diazoacetate **12** together with the ligand bearing *tert*-butyl substituents **292**.[74] Both enantioselectivity and diastereoselectivity increased by using a bulkier diazoester, such as *tert*-butyl diazoacetate **133** or (1*R*,2*S*,5*R*)-menthyl diazoacetate ((1*R*,2*S*,5*R*)-**144**, up to 98% *ee* in *trans*-cyclopropanes with 14/86 *cis*/*trans*-diastereoselectivity. The best conditions were applied to other alkenes, also with excellent results.

Similar results were also described by Evans and coworkers using the same ligand, and also the closely related bis-oxazoline ligands bearing an isopropylidene bridge, instead of the methylene **293**.[142] Using the bulky BHT diazoacetate **168** (BHT = 2,6-di-*tert*-butyl-4-methylphenyl), up to 99% *ee* in *trans*-cyclopropanes with 6/94 *cis*/*trans*-diastereoselectivity and 85% yield was obtained, which represents 93% of a single stereoisomer out of four possible products, using only 1 mol% catalyst (Table 38).[142]

Table 38 Results obtained in the cyclopropanation of **10** with alkyl diazoesters, catalyzed by chiral bisoxazoline–copper complexes



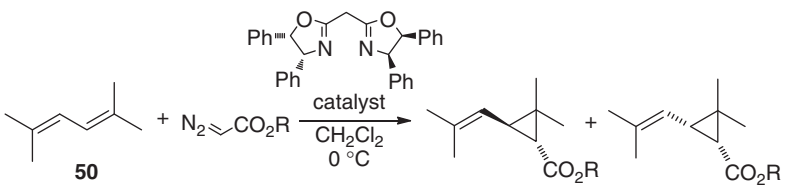
292

293

Ligand	*Diazoester*	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
292	**12**	77:23	98	93	n.d.
293	**12**	73:27	99	97	77
293	**133**	81:19	96	93	75
293	**221**	86:14	97	96	68
293	**168**	94:6	99	n.d.	85

The best ligand for the cyclopropanation of styrene **10** showed to be inadequate for the enantioselective cyclopropanation of 2,5-dimethyl-2,4-hexadiene **50**. In this case, the ligand bearing four stereogenic centers with four phenyl groups **294** was by far superior.[410] With the bulky dicyclohexylmethyl diazoacetate **221** at 0 °C, up to 94% *ee* in *trans*-cyclopropanes with 5:95 *cis*/*trans*-diastereoselectivity and 78% yield was described (Table 39).

Table 39 Results obtained in the cyclopropanation of **50** with alkyl diazoesters, catalyzed by the **294**–copper complex



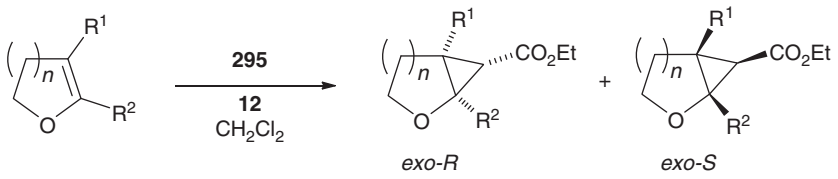
50

R	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
2,3,4-Trimethyl-3-pentyl	85:15	88	n.d.	76
(1*S*,2*R*,5*S*)-Menthyl	86:14	90	78	70
(1*R*,2*S*,5*R*)-Menthyl	92:8	92	84	72
2,4-Dimethyl-3-pentyl	93:7	94	n.d.	78
2,6-Di-*tert*-butyl-4-methylpehenyl	94:6	94	n.d.	75
Dicyclohexylmethyl	95:5	94	n.d.	78

However, copper complexes of the Evans ligand **293** have proven to be among the best ones also in the enantioselective cyclopropanation of other alkene substrates, so they can be qualified as one of the best synthetic methods available for

cyclopropanes. Thus, the enantioselective cyclopropanation of cyclic enol ethers was carried out with the **293**–CuOTf complex **295** with excellent results when the double bond was trisubstituted. Up to 95% diastereoselectivity and 96% enantioselectivity could be obtained in the best case (i.e., more than 91% of a single stereoisomer out of four possible) (Table 40).[833]

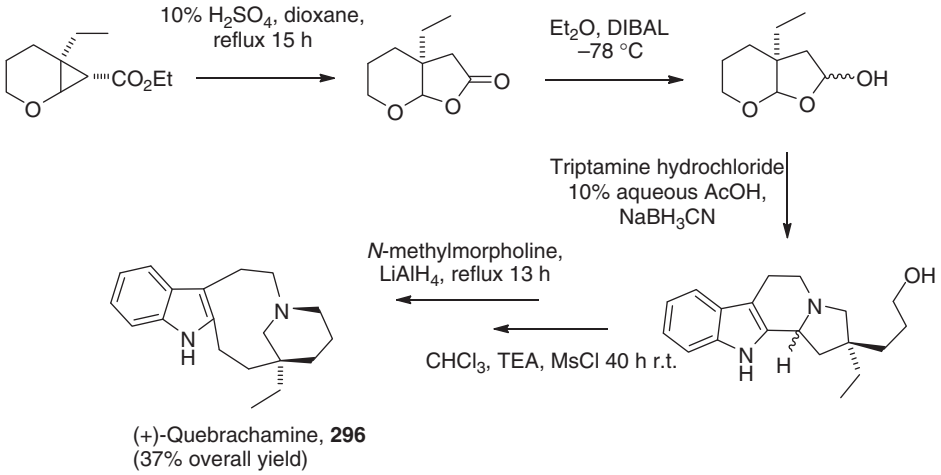
Table 40 Results obtained in the cyclopropanation of cyclic enol ethers with **12**, catalyzed by **295**



R^1	R^2	n	endo:exo	ee exo (%)[a]	Yield (%)
Me	H	1	30:70	>95	60
Et	H	1	28:72	>95	57
CH_2Ph	H	1	21:79	96	77
Et	H	2	9:91	>95	52
Pr^n	H	2	6:94	>95	54
CH_2Ph	H	2	5:95	96	67
H	CH_2Ph	2	7:93	74[b]	45

[a] *exo-R* is the major enantiomer.
[b] *exo-S* is the major enantiomer.

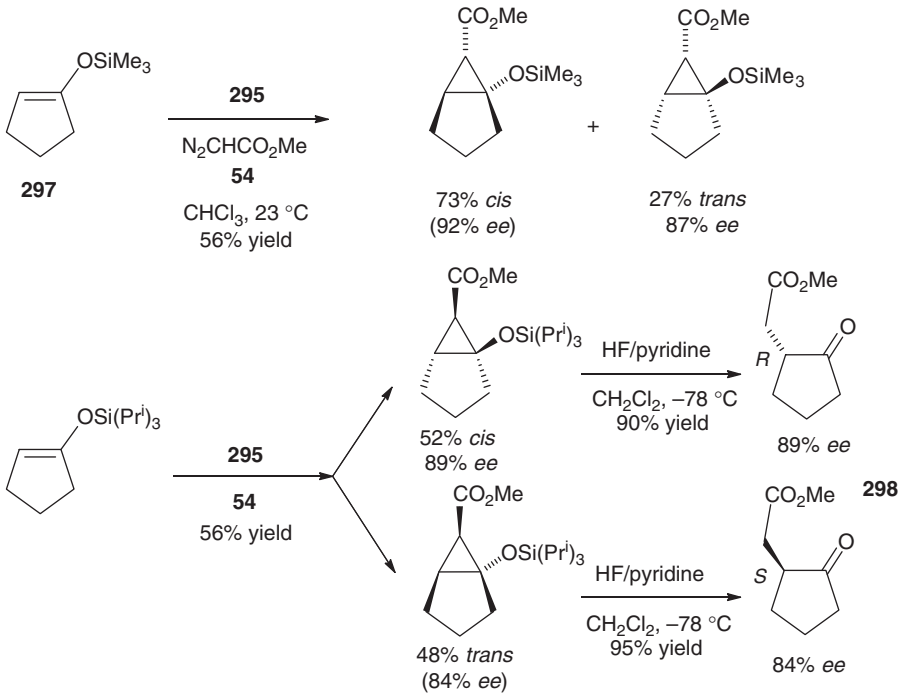
From one of the cyclopropane products, the indole alkaloid (+)-quebrachamine **296** was synthesized, which served to show the synthetic usefulness of the procedure, and also to determine the absolute configuration of the major cyclopropane intermediate obtained (Scheme 32).



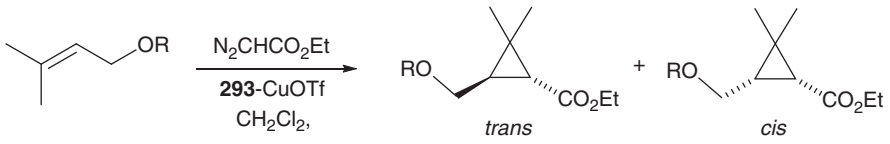
Scheme 32

Silyl enol ethers have also been used as substrates for cyclopropanation with this catalytic system, leading to synthetically useful cyclopropane intermediates. The enantioselective cyclopropanation of 1-(trimethylsilyloxy)cyclopentene **297** could be carried out with up to 92% *ee* in the major diastereomeric cyclopropane. The cyclopropane intermediates could subsequently be transformed into chiral cyclic γ-ketocarboxylates **298** (Scheme 33).[808] Curiously, the same catalyst showed low enantioselectivity in the case of the six-membered ring analog 1-(trimethylsilyloxy)-cyclohexene **299**. In this case, aza-semicorrin–Cu(OTf) complex led to better enantioselectivity.

The same catalyst has also been tested in the cyclopropanation of trisubstituted alkenes, structurally derived from allyl alcohol, which are interesting substrates to obtain pyrethroids. In the best case, a *trans*/*cis* ratio of 91:9, with 92% *ee* for the major isomer was obtained from the reaction of the *p*-methoxybenzoate derivative. The highest *ee* was 95%, for the *trans*-cyclopropane of an 80:20 diastereomer mixture (acetate derivative).[834]



Scheme 33

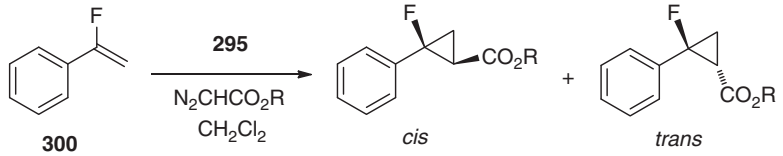


R = Ac	–6 °C, 50% yield	80% (95% *ee*)	20% (47% *ee*)
benzyl	0 °C, 74% yield	88% (93% *ee*)	12% (% *ee* n.d.)
benzoyl	0 °C, 82% yield	82% (92% *ee*)	18% (% *ee* n.d.)
p-MeObenzoyl	0 °C, 61% yield	91% (92% *ee*)	9% (12% *ee*)

(82)

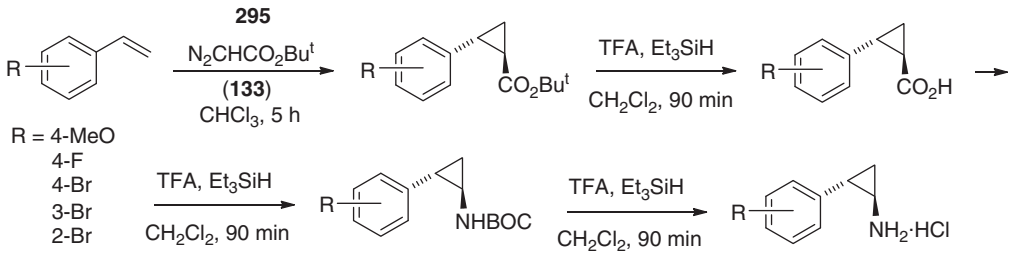
Another synthetic application of this catalytic system has been described in the cyclopropanation of α-fluorostyrene **300**, to give the corresponding *cis*-2-fluoro-2-phenylcyclopropane carboxylate **301**, subsequently transformed into the enantiopure *cis*-2-fluoro-2-phenylcyclopropylamine **302**, which is a key intermediate in the syntheses of antibacterial quinolones, analogous to the highly potent antibiotic ciprofloxacin (**303** Ciprobay®).[835,836] In this case, the use of bulky diazoesters was required to guarantee a good stereoselectivity (diastereo- and enantioselectivity) toward the desired intermediate (Table 41).

Table 41 Results obtained in the cyclopropanation of **300** with alkyl diazoesters, catalyzed by **295**



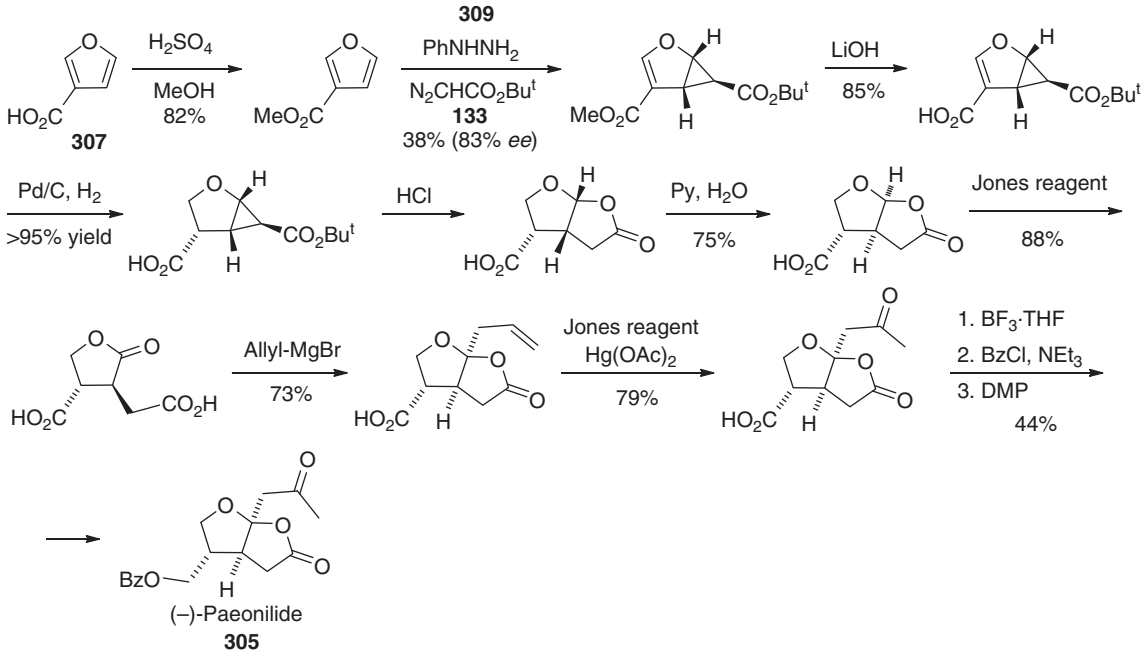
R	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Et	28:72	80	89	62
Bu^t	19:81	89	93	56
l-Menthyl	19:81	>98	92	28

A similar strategy has been used to prepare the related *trans*-2-phenylcyclopropylamine **304**, (tranylcypromine), a known monoaminooxidase inhibitor, used as antidepressant and anxiolytic, as well as some analogs bearing substituents at the phenyl ring (Scheme 34).[837]



Scheme 34

Another synthetic application of this catalyst is the preparation of (−)-paeonilide (**305**) starting from 3-furancarboxylic acid **307**.[838] The stereogenic centers of the final product come from the enantioselective cyclopropanation step. In this case, the best results were obtained with the complex of the analogous bisoxazoline ligand bearing isopropyl groups **308** with $Cu(OTf)_2$ **309** (Scheme 35).



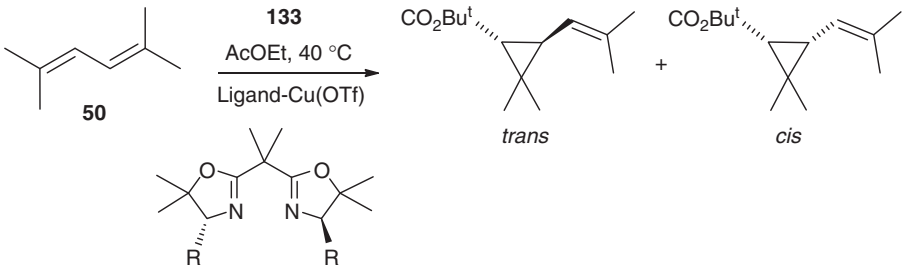
Scheme 35

As a logical consequence of the good performance of bisoxazoline-copper catalysts, some modifications to the initial structure of these chiral ligands have been described. In some cases, modifications only modify steric congestion around the metal, keeping the main structure of the ligand. In other cases, modifications affect the bridge between both oxazoline moieties. Finally, in some cases, new stereogenic elements have been introduced in the bisoxazoline structure. It can be acknowledged that in many occasions, changes in the ligand structure do not improve, and even worsen the enantioselectivity results in cyclopropanation reactions, although they can be important for other different catalytic transformations. Here only those modifications leading to good results in the title reactions are included.

As already commented, ligand **293** is not suitable for the efficient cyclopropanation of **50**, the best results being obtained using a bisoxazoline with four stereogenic centers.[410] Itagaki and coworkers described a series of sterically crowded bisoxazoline ligands for this reaction. In general, very good yields were obtained in the desired products, and when **133** was used as the carbene source, good diastereo- and enantioselectivities were also achieved (Table 42).[839]

C_2-symmetry is not mandatory to obtain good enantioselectivities with bisoxazoline ligands. García and coworkers demonstrated this by synthesizing a series of C_1-symmetric bisoxazoline ligands with one or two stereogenic centers. When one of the oxazoline rings bears a *tert*-butyl substituent at the 4-position, even a small substituent at the 4′-position in the other ring is

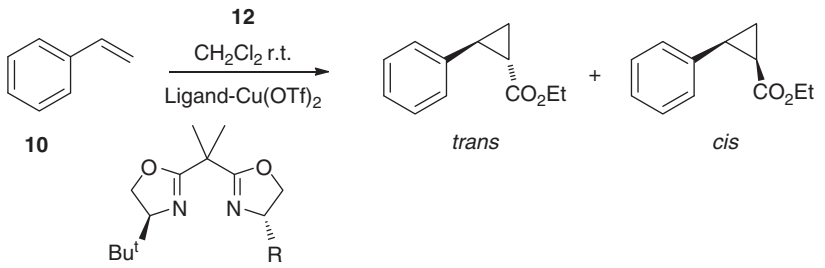
Table 42 Results obtained in the cyclopropanation of **50** with alkyl diazoesters, catalyzed by some substituted bisoxazoline–Cu catalysts



R	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	84:16	88	68	93
2-$MeOC_6H_4$	85:15	93	69	88
1-Naphthyl	86:14	95	69	92
2-Naphthyl	79:21	85	69	91

enough to lead to good enantioselectivities in the benchmark cyclopropanation reaction. Theoretical calculations helped to explain this rather surprising result (Table 43).[405]

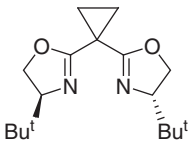
Table 43 Results obtained in the cyclopropanation of **10** with **12**, catalyzed by bisoxazoline–copper complexes



R	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Bu^t	71:29	94	91	72
H	68:32	29	8	58
Me	67:33	84	79	74
CH_2Ph	64:36	83	75	73
Ph	72:28	82	69	79

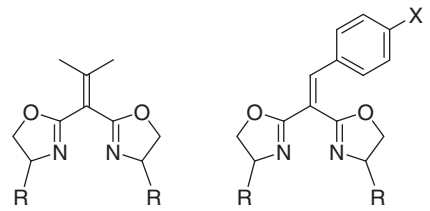
Other structural modifications introduced in bisoxazoline ligands concern the bridge between the two oxazoline rings. Originally, this bridge was a methylene or isopropylidene group. However, other carbon and heteroatom-bearing groups have been used to link both moieties, and even to introduce a new one, as will be seen below.

For instance, Itagaki and coworkers described the replacement of the isopropylidene bridge by a cyclopropylidene group **310**. When this ligand was tested in the benchmark cyclopropanation reaction of styrene **10** with ethyl diazoacetate **12**, increased diastereoselectivity (from 75:25 to 86:14) and enantioselectivity (from 99% *ee* to >99.9% *ee*) with regard to the original ligand was obtained with only 0.1 mol% catalyst.[424]

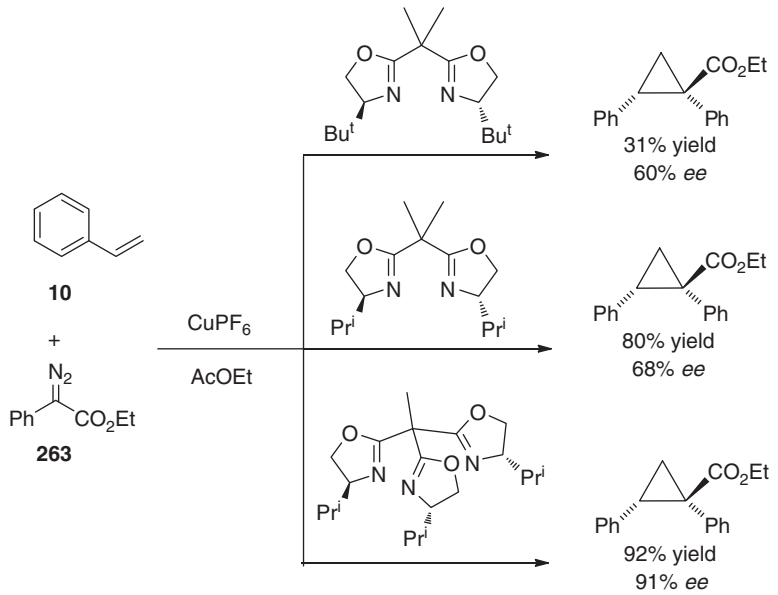


310

Less successful was the use of alkylidene or arylidene bridging groups, described by Burke and coworkers. In these cases, only moderate enantioselectivities, inferior to those obtained with the Evans ligand, could be achieved.[400,840]



Another modification described is the introduction of a third oxazoline ring, as a sidearm, leading to trisoxazoline ligands, which can be C_3-symmetrically substituted or not. When this kind of ligand is used in the cyclopropanation of styrene **10** with ethyl phenyldiazoacetate **263**, better yields and enantioselectivities are obtained, compared with those of the Evans ligand (Scheme 36). Using a nonsymmetrically substituted trisoxazoline ligand, bearing two isopropyl and one *tert*-butyl group **311**, very good yields and good enantioselectivities were obtained in a variety of structurally different alkenes (Table 44).[152]

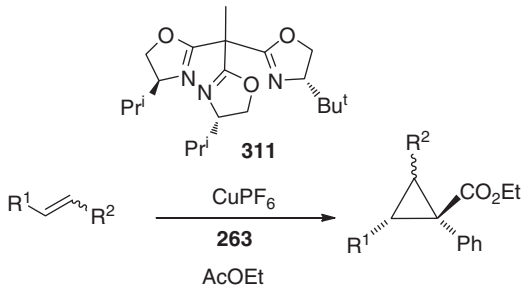


Scheme 36

Bridges containing heteroatoms have also been described and tested. Similar to what happened with semicorrins and aza-semicorrins, imino bridges have also been described in the case of bisoxazoline ligands, leading to the so-called aza-bisoxazolines. These ligands were first described by Reiser and coworkers,[418] and cyclopropanation of styrene **10** with methyl diazoacetate **54** was one of the first reactions tested. The aza-bisoxazoline bearing *tert*-butyl substituents **312**, analogous to the Evans bisoxazoline, led to good enantioselectivities, both with **10** and 1,1-diphenylethene **108**, but somewhat lower than those obtained with bisoxazoline. The original aza-bisoxazoline ligand was *N*-methylated at the imino nitrogen atom. However, in a subsequent work, it was shown that the *N*-benzylation of the bridging nitrogen leads to enantioselectivity results much closer to those obtained with the Evans bisoxazoline (Table 45).[420]

Other polytopic variants of these types of ligands, bearing two or three aza-bisoxazoline units in the same molecule, have been described and tested with excellent results in cyclopropanation reactions.[419,420]

Table 44 Results obtained in the cyclopropanation of alkenes with **263**, catalyzed by the **311**–$CuPF_6$ complex



Alkene	*Temperature (°C)*	ee *(%)*	*Yield (%)*
Ph	40	92	92
p-ClC_6H_4	40	91	97
p-MeC_6H_4	40	93	99
p-$MeOC_6H_4$	40	95	94
Ph	40	89	99
	40	87	85
Ph	40	82	51
BuO	20	82	99
O	20	83	80
O	20	90	86

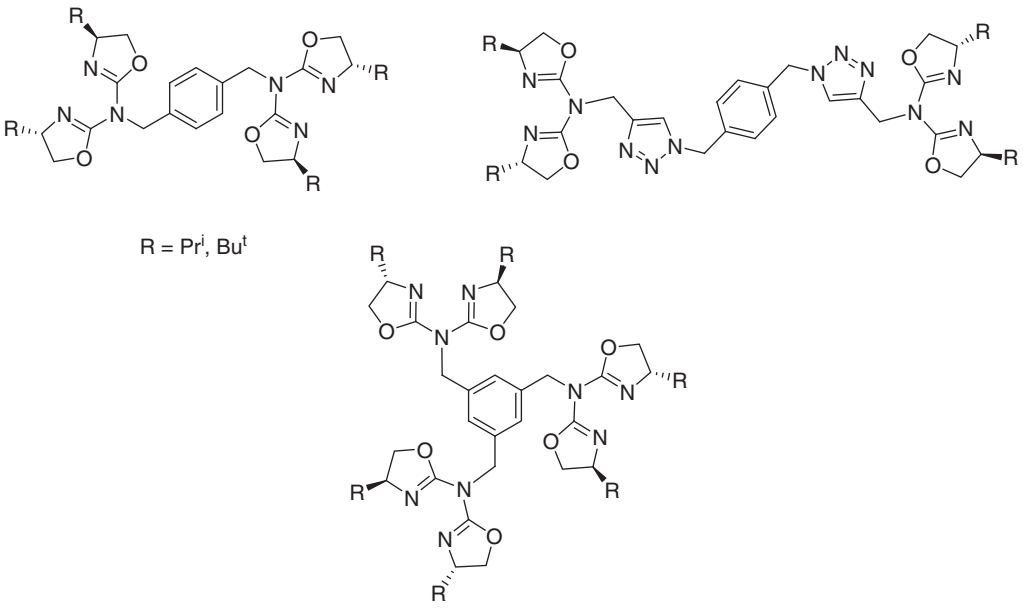
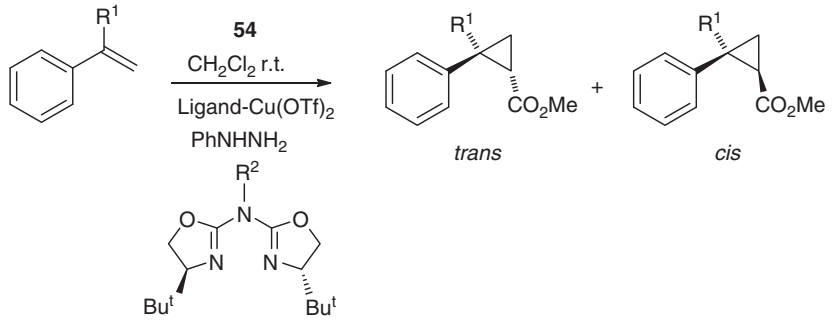
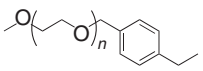
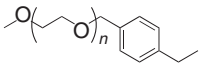


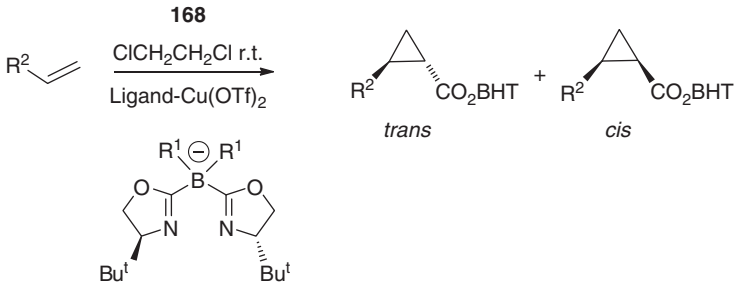
Table 45 Results obtained in the cyclopropanation of **10** and **108** with **54**, catalyzed by aza-bisoxazoline–copper complexes



R^1	R^2	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Me	H	73:27	92	84	82
	H	71:29	91	87	69
Me	Ph	–	83		41
	Ph	–	90		73
CH_2Ph	H	70:30	98	90	54

Chiral boron-bridged bisoxazolines have been described by Pfaltz and coworkers.[417] The presence of a tetrasubstituted boron atom makes this ligand anionic, similar to what happened with semicorrins, so neutral complexes are formed with Cu(I) salts. The so-called borabox ligands were tested in the enantioselective cyclopropanation of styrene and other alkenes with alkyl diazoacetates. In general, results were inferior to those obtained with the analogous bisoxazoline ligands, and only the use of bulky diazoesters, like 2,6-di-*tert*-butyl-4-methylphenyl (BHT) diazoacetate **168**, allowed obtaining good stereoselectivities (Table 46).

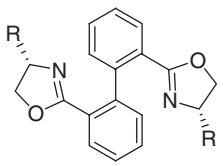
Table 46 Results obtained in the cyclopropanation of alkenes with **168**, catalyzed by borabox–copper complexes



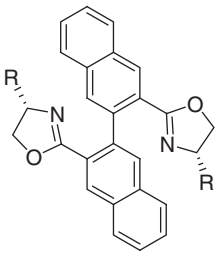
R^1	R^2	trans:cis	ee trans *(%)*	*Yield (%)*
Me	Ph	96:4	99	85
Ar_F[a]	Ph	99:1	98	89
Me	*p*-$MeOC_6H_4$	96:4	96	35
Ar_F	*p*-$MeOC_6H_4$	96:4	97	65
Me	*p*-FC_6H_4	96:4	99.4	89
Ar_F	*p*-FC_6H_4	99:1	99.5	91
Me	$PhCH_2$	93:7	99	n.d.
Ar_F	$PhCH_2$	92:8	97	66
Me	*n*-Hexyl	98:2	99	51
Ar_F	*n*-Hexyl	99:1	95	68

[a] Ar_F = 3,5-bis(trifluoromethyl)phenyl.

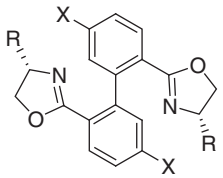
Introduction of additional stereogenic elements in the bisoxazoline ligands has been achieved using several strategies, for instance, by using chiral bridging elements, as tartaric acid derivatives,[388] but, in general, they do not have improved the results obtained with traditional bisoxazoline ligands in cyclopropanation reactions. A special family that deserves comment in this regard is that of axially chiral bisoxazoline ligands, in which the additional stereogenic element is an axis belonging to a biphenyl or a binaphtyl moiety.[394,403,412,414,415] As in precedent cases, enantioselectivity results only can be improved by using bulky diazoesters, like menthyl diazoacetate **144**.



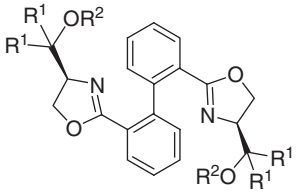
R = Pr^i, Bu^t



R = Bu^t



R = Pr^i, Bu^t
X = Cl, Ph



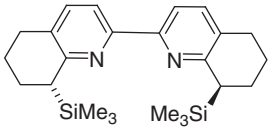
$R^1 = R^2 = H$
$R^1 = R^2 = Me$
$R^1 = R^2 = Et$

Some reviews have been published dealing with the immobilization of these kinds of ligands using covalent and noncovalent immobilization strategies, and organic, inorganic, and composite supports.[841,842]

Another family of chiral bidentate NN ligands whose copper complexes have been used in enantioselective cyclopropanation reactions is that of bipyridines. As in the case of bisoxazolines, most of the chiral bipyridine ligands tested are C_2-symmetric, although some examples of asymmetric ligands have been reported.

First examples of these systems in cyclopropanation reactions were described by Katsuki and coworkers,[330,331] with moderate enantioselectivities in the benchmark reaction of styrene **10** with *t*-butyl diazoacetate **133**. By modifying the former structure, introducing bulkier groups at the stereogenic centers, the same researchers were able to improve the enantioselectivity values in the same reaction, up to 92% *ee* in the major *trans*-cyclopropane. Good results were also obtained with other alkenes. The use of **133** also led to good *trans*/*cis*-diastereoselectivities, *trans*-cyclopropanes being highly favored (**Table 47**).[332]

Table 47 Results obtained in the cyclopropanation of alkenes with **133**, catalyzed by the **313**–copper complex

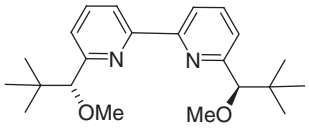


313

Alkene	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
p-Chlorostyrene **163**	82:18	95	98	72
Styrene **10**	86:14	92	98	75
p-Methoxystyrene	90:10	83	>99	73
1-Octene	85:15	91	–	65
1-Phenylbutadiene	70:30	83	89	90
(*Z*)-*β*-Methylstyrene	>99:1	73	–	94
(*E*)-*β*-Methylstyrene	40:60	24	>99	54

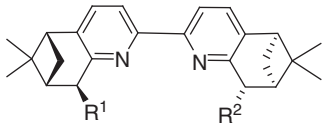
Kwong et al. described a chiral bipyridine bearing two chiral stereocenters attached to free-rotating substituents **314**.[335] Moderate to good enantioselectivities were obtained with Cu(I) and Cu(II) complexes of this ligand in several reactions of styrenes

with ethyl diazoacetate **12**. As in precedent cases, both *cis*/*trans*-diastereoselectivity and enantioselectivity could be slightly improved by using the bulkier *tert*-butyl diazoacetate **133**. For instance in the reaction of styrene, the passing from **12** to **133** results in an improvement of *trans*/*cis*-diastereoselectivity from 80:20 to 90:10, and of enantioselectivity in *trans*-cyclopropanes from 89% to 92% *ee*.



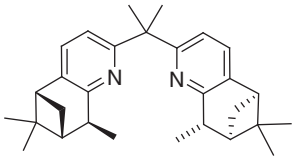
314

In most cases, however, the stereogenic centers are attached to condensed cycles, as in the case of the former ligands described by Katsuki and Ito. In this sense, terpenes have often been used as starting compounds to obtain chiral bipyridine ligands. For instance, Lötscher and coworkers used (−)-*β*-pinene **315** as starting point to obtain a series of bipyridine ligands **316**.[340] Only in some cases, moderate to good enantioselectivities were obtained in the benchmark cyclopropanation reaction of **10** with **12** (up to 90% *ee* in *trans*-cyclopropanes and 87% *ee* in *cis*-cyclopropanes, with 78:22 *trans*/*cis*-diastereoselectivity when the ligand with $R^1 = R^2 = Et$ is used).



316

Chelucci and coworkers used a similar strategy, starting from **315** and (−)-isopinocampheol **318**, but to synthesize dipyridylmethane ligands, instead of bipyridines.[341] In all but one case, poor enantioselectivity results were obtained in the benchmark cyclopropanation reaction. The best results (88% *ee* in *trans*-cyclopropanes and 79% *ee* in *cis*-cyclopropanes) were obtained with ligand **319**. These results were even slightly better than those obtained with the analogous bipyridine ligand **316** ($R^1 = R^2 = Me$).[340]



319

Terpenes have also been used to introduce chirality in the structurally related terpyridine ligands.[90,350] Moderate to good enantioselectivities were described in the cyclopropanation of styrenes with alkyl diazoacetates, above all when the latter bear bulky alkyl groups (**Table 48**).

More recently, another bipyridine ligand has been described by Lyle and Wilson, in which the stereogenic centers are introduced by asymmetric catalytic dihydroxylation with AD-mix-*β*.[139] Good enantioselectivities (up to 99% *ee*) are obtained with this ligand in the cyclopropanation of styrene, above all when using *tert*-butyl diazoacetate **133**, which also leads to excellent *cis*/*trans*-diastereoselectivities (more than 10:90 in most cases).

A similar strategy has been described by Boyd et al., who used a dioxygenase-catalyzed dihydroxylation to obtain the chiral precursors of bipyridine ligands structurally related with the precedent ones.[346] These ligands also lead to good results in the same cyclopropanation reaction of styrenes with **133** (**Table 49**).

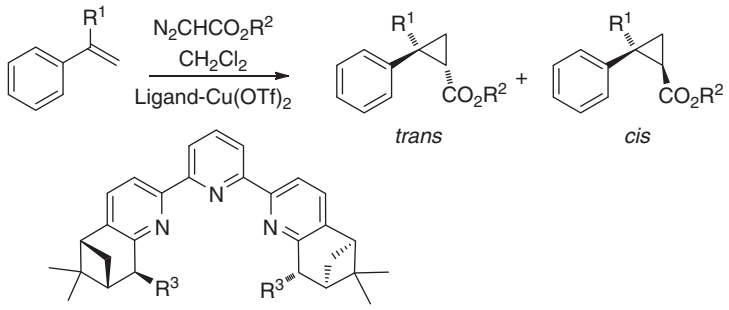
In some cases, the bipyridine ligands do not bear any stereogenic center, but the chirality comes from a stereogenic axis or a stereogenic plane. Fu and coworkers described a planar chiral ligand bearing two ferrocenyl substituents.[338] Using 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate **168**, good diastereoselectivities and enantioselectivities were obtained in several cyclopropanation of alkenes. This bipyridine ligand is structurally related with the planar chiral bisazaferrocene, formerly described by the same group,[843] which also led to similar selectivity results (**Table 50**).

Axially chiral atropoisomeric bipyridine ligands have also been described and tested in cyclopropanation reactions, leading to moderate enantioselectivities in cyclopropanation reactions of styrenes with ethyl diazoacetate (**Table 51**).[339]

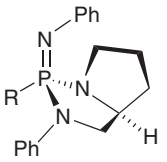
Apart from these families of chiral ligands used with copper, some other particular examples have been described with less common chiral ligands, which will be revised next.

Brunel et al. described some chiral iminodiazaphospholidines whose copper complexes displayed good diastereo and enantioselectivities in the cyclopropanation reactions with ethyl diazoacetate **12** (up to 98% in *trans*-cyclopropanes with 94% *ee* with styrene **10** and 100% in *trans*-cyclopropanes with 95% *ee* with 1-vinylnaphthalene **321**).[722]

Table 48 Results obtained in the cyclopropanation of **10** and **108** with diazoesters, catalyzed by terpyridine–copper complexes

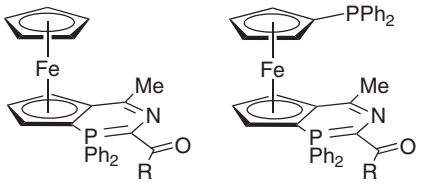


R^1	R^2	R^3	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
H	Et	H	78:22	30	29	98
H	Et	Me	64:36	75	84	98
H	Et	Pr^i	59:41	40	51	98
H	Et	Bu^n	68:32	86	90	98
H	Et	CH_2Ph	61:39	72	75	97
H	Bu^t	Bu^n	77:23	85	90	91
H	(1*R*,2*S*,5*R*)-menthyl	Bu^n	75:25	76	83	90
H	(1*S*,2*R*,5*S*)-menthyl	Bu^n	91:9	83	58	89
Ph	Bu^t	Bu^n	–	79	92	



R = NMe_2, Ph

1,2-Ferrocenediylazaphosphinines are chiral planar ligands, whose copper complexes lead in general to low enantioselectivities.[791] However, when the alkene used was 1,1-diphenylethene **108**, up to 90% *ee* could be obtained with *tert*-butyl diazoacetate **133**, and >99% *ee* with BHT diazoacetate **168**, as a function of the ligand used (R = H).



R = H, Me, Ph

C_2-symmetric bis(ephedrine)–copper complexes have also been tested in the benchmark cyclopropanation reaction of styrene **10** with ethyl diazoacetate **12**. In general, only moderate stereoselectivities are obtained with these catalysts.[844]

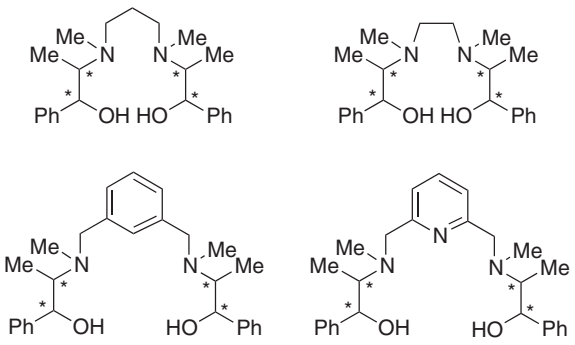
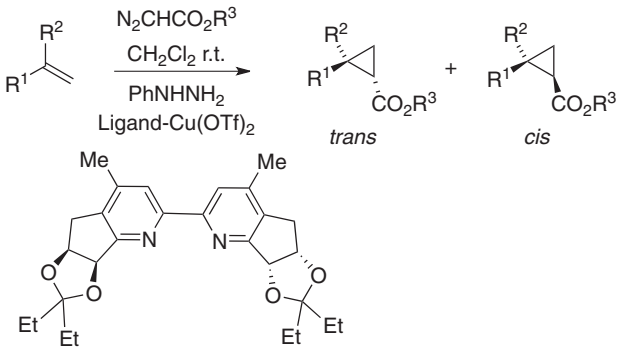
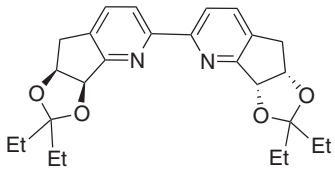


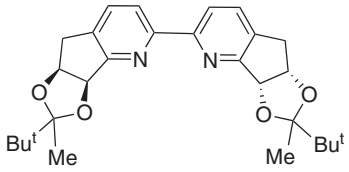
Table 49 Results obtained in the cyclopropanation of alkenes with diazoesters, catalyzed by bipyridine–copper complexes



R^1	R^2	R^3	trans:cis	ee trans *(%)*	*Yield (%)*
Ph	H	Et	80:20	82	74
Ph	H	CH_2Ph	92:8	84	49
Ph	H	Bu^t	93:7	92	67
Ph	H	Bu^t	92:8	93	68
p-$MeOC_6H_4$	H	Bu^t	>95:5	71	69
p-FC_6H_4	H	Bu^t	92:8	99	73
$PhCH_2CH_2$	H	Bu^t	>95:5	83	82
Ph	Ph	Bu^t	–	72	81



Ph	H	Bu^t	–[a]	88	91
p-$MeOC_6H_4$	H	Bu^t	–[a]	91	90



Ph	H	Bu^t	–[a]	92	97
p-$MeOC_6H_4$	H	Bu^t	–[a]	95	97

[a] *trans/cis* from 90:10 to 97:3.[346]

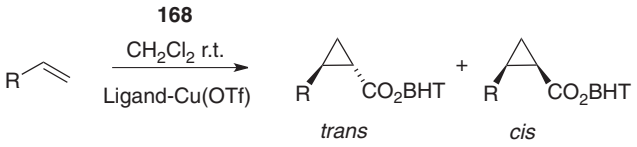
Finally, chiral dihydrodinaphthazepinyl–oxazoline ligands have been also tested in the copper-catalyzed enantioselective cyclopropanation of olefins with diazoacetates.[845] In general, moderate enantioselectivities are obtained using bulky diazoesters, like menthyl diazoacetate **144**. Unfortunately, the best enantioselectivities are obtained in minor *cis*-cyclopropanes (Table 52).

4.20.4.1.5.2.2 Rhodium catalysts

Chiral dirhodium carboxylates have been used in the enantioselective cyclopropanation of alkenes with diazoesters. The former works, most of them carried out by Davies and coworkers, used rhodium(II) *N*-arylsulphonyl prolinate complexes. Although in the first works the use of vinylcarbenoids led to good stereoselectivity results,[507] only in the mid-1990s these good diastereoselectivities and enantioselectivities could be extended to alkyl aryldiazoacetates (Table 53).[212]

Thus, excellent *trans*/*cis*-diastereoselectivities (up to 98:2) and good enantioselectivities (up to 88% *ee*) could be obtained using methyl phenyldiazoacetate as the ketocarbenoid precursor. In a further work, these good results were extended to other aryldiazoacetates and styrenes, including 1,1-diphenylethene **108**, with the catalyst bearing the *p*-dodecylphenyl substituent (Rh_2(*S*-DOSP)$_4$ **42**).[513]

Table 50 Results obtained in the cyclopropanation of alkenes with **168**, catalyzed by planar chiral aza-ligands–copper complexes



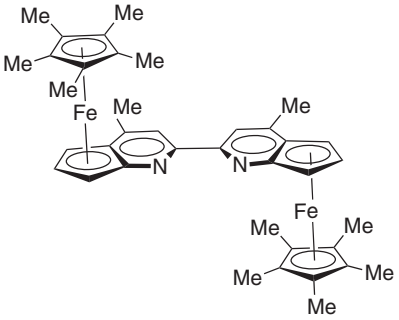
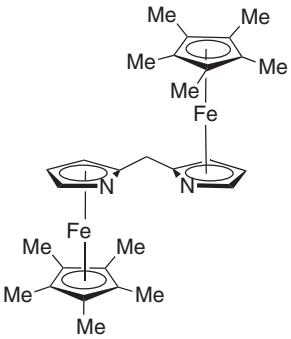
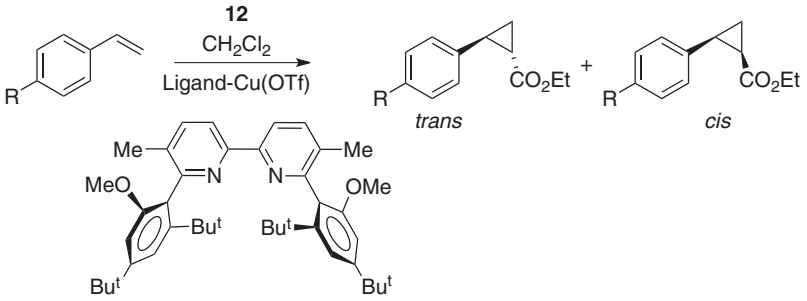
Ligand	R^1	trans:cis	ee trans *(%)*	*Yield (%)*
	Ph	97:3	87	78
	p-$MeOC_6H_4$	95:5	75	71
	p-$CF_3OC_6H_4$	94:6	94	83
	n-Hexyl	94:6	78	78
	Et_3Si	96:4	80	60
	Ph	96:4	94	79
	p-$CF_3OC_6H_4$	94:6	96	81
	p-$MeOC_6H_4$	94:6	87	90
	$PhCH_2$	94:6	91	78
	n-Hexyl	93:7	90	80
	Et_3Si	99:1	95	64

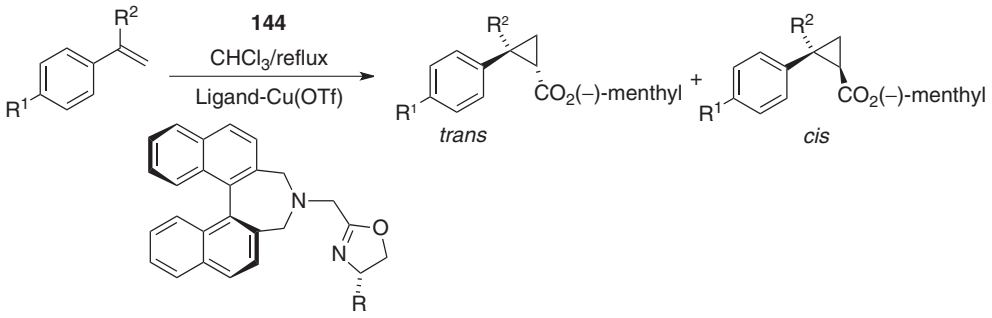
Table 51 Results obtained in the cyclopropanation of *p*-substituted styrenes with **12**, catalyzed by an atropoisomeric bipyridine–copper complex



R	*Time (h)*	trans:cis	ee trans *(%)*	*Yield (%)*
OMe	6	86:14	74	81
Me	6	85:15	76	86
H	8	85:15	80	80
Cl	18	86:14	84	78

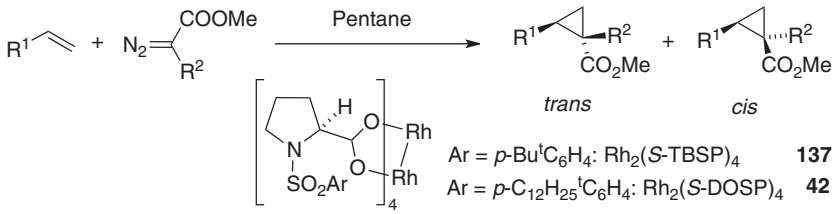
Although **42** is the most employed catalyst, some structurally related chiral ligands have been prepared and tested by Davies and coworkers. For instance, linking two *N*-arylsulfonyl prolinate moieties into a single ligand has provided improved results in the reactions of methyl 2-diazo-4-phenylbut-3-enoate **235** and methyl phenyldiazoacetate **39** with styrenes (Table 54).[532]

Table 52 Results obtained in the cyclopropanation of styrenes with **144**, catalyzed by dihydrodinaphthazepinyl–oxazoline–copper complexes



R^1	R^2	R	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
H	H	CH_2Ph	75:25	81	86	93
Me	H	Ph	70:30	71	87	80
OMe	H	Ph	67:33	65	79	85
Cl	H	Ph	71:29	91	90	79
H	Me	Ph	58:42	91	88	79

Table 53 Results obtained in the cyclopropanation of alkenes with α-substituted methyl diazoacetates, catalyzed by Rh_2(*S*-TBSP)$_4$ **137** and Rh_2(*S*-DOSP)$_4$ **42**



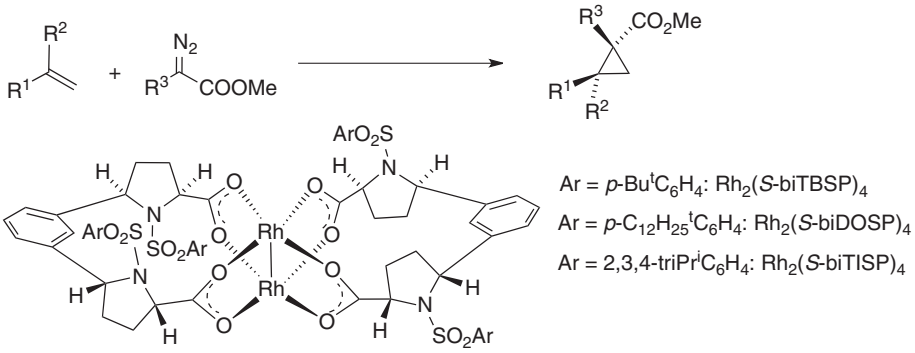
R^1	R^2	*Catalyst*	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	CH═CHPh	Rh_2(*S*-TBSP)$_4$	98:2	90	n.d.	91
Ph	CH═CHPh	Rh_2(*S*-DOSP)$_4$	98:2	94	n.d.	91
Ph	H	Rh_2(*S*-TBSP)$_4$	55:45	6	30	80
Ph	COMe	Rh_2(*S*-TBSP)$_4$	75:25	5	8	57
Ph	CO_2Me	Rh_2(*S*-TBSP)$_4$	–	7	63	
Ph	Me	Rh_2(*S*-DOSP)$_4$	80:20	12	58	45
Ph	Ph	Rh_2(*S*-TBSP)$_4$	98:2	87	n.d.	90
p-$MeOC_6H_4$	Ph	Rh_2(*S*-TBSP)$_4$	98:2	88	n.d.	82
p-ClC_6H_4	Ph	Rh_2(*S*-TBSP)$_4$	98:2	85	n.d.	84
OEt	Ph	Rh_2(*S*-DOSP)$_4$	97:3	66	n.d.	88
OBu	Ph	Rh_2(*S*-DOSP)$_4$	97:3	64	n.d.	84
OEt	Ph	Rh_2(*S*-DOSP)$_4$	93:7	80	n.d.	86
Bu	Ph	Rh_2(*S*-DOSP)$_4$	93:7	77	n.d.	86
Pr^i	Ph	Rh_2(*S*-DOSP)$_4$	87:13	74	n.d.	63
CH_2OAc	Ph	Rh_2(*S*-DOSP)$_4$	97:3	80	n.d.	85

Dirhodium tetraprolinates have also successfully applied to the reaction of ketocarbenes with cyclopolyenes, such as cycloheptatriene and 1,3-cycloheptadiene.[514]

Fluorinated compounds display a special interest in biomedical applications, and for this reason, α-fluorostyrene **300** has also been tested as a substrate in this kind of cyclopropanation reaction.[523] Good yields and enantioselectivities have been reported, although *trans*/*cis*-diastereoselectivities are somewhat lower than those obtained with normal styrenes (Table 55).

Moreover, due to their synthetic interest, *N-tert*-butoxycarbonyl (BOC) protected alkenylamines have been tested as substrates for the reaction with vinyl diazoesters, catalyzed by Rh_2(*S*-DOSP)$_4$ **42**. In this case, the C–H insertion reaction competes with the cyclopropanation, leading to a significant proportion (about one-third of the total yield) of insertion products. Excellent enantioselectivities were obtained both for cyclopropanes and C–H insertion products (Table 56).

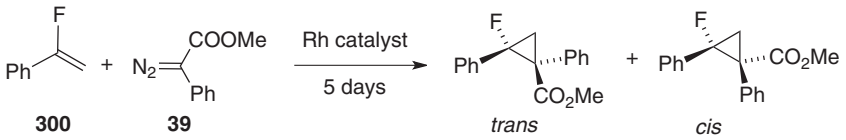
Table 54 Results obtained in the cyclopropanation of alkenes with α-substituted methyl diazoacetates, catalyzed by chiral dirhodium carboxylates



R[1]	*R*[2]	*R*[3]	*Catalyst*	*Temperature (°C)*	ee *(%)*	*Yield (%)*
Ph	H	CH=CHPh	Rh_2(*S*-bi-TBSP)$_4$	25	63	–[b]
Ph	H	CH=CHPh	Rh_2(*S*-bi-DOSP)$_4$	25	68	–[b]
Ph	H	CH=CHPh	Rh_2(*S*-bi-TISP)$_4$	25	90	–[b]
Ph	H	CH=CHPh	Rh_2(*S*-bi-TISP)$_4$	–50	98	–[b]
Ph	H	CH=CHPh	Rh_2(*S*-bi-DOSP)$_4$	25	74[a]	–[b]
Ph	H	CH=CHPh	Rh_2(*S*-bi-DOSP)$_4$	–50	88[a]	–[b]
OEt	H	CH=CHPh	Rh_2(*S*-bi-TISP)$_4$	–50	87	53
OEt	H	Ph	Rh_2(*S*-bi-TISP)$_4$	–50	79	86
Ph	Ph	CH=CHPh	Rh_2(*S*-bi-TISP)$_4$	25	91	94
Ph	Ph	CH=CHPh	Rh_2(*S*-bi-TISP)$_4$	–50	>97	32
Ph	Ph	Ph	Rh_2(*S*-bi-TISP)$_4$	–50	>97	81

[a]The absolute configuration is (*R*,*R*), opposite to that obtained with the other catalysts.
[b]Yields ranging from 52% to 92%.

Table 55 Results obtained in the cyclopropanation of **300** with **39**, catalyzed by chiral dirhodium carboxylates



300 **39** *trans* *cis*

Catalyst	*Temperature (°C)*	trans:cis	ee *(%)*	*Yield (%)*
Rh_2(*S*-TBSP)$_4$	25	25:75	78	63
Rh_2(*S*-TISP)$_4$	–78	21:79	84	81
Rh_2(*S*-DOSP)$_4$	25	26:74	80	79
Rh_2(*S*-DOSP)$_4$	–78	25:75	>99	91

Although Rh_2(*S*-DOSP)$_4$ **42** and Rh_2(*S*-TBSP)$_4$ **137** catalysts have been successfully used in many instances, some structurally related catalysts have also been tested. For instance, more rigidity in the pyrrolidine ring of the prolinate moiety has been introduced by using an azanorbornane instead.[533] However, the results obtained with this chiral ligand do not outperform those obtained with the former ones.

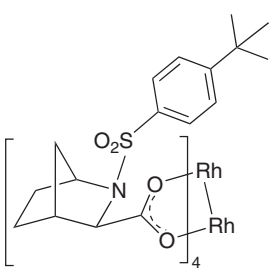
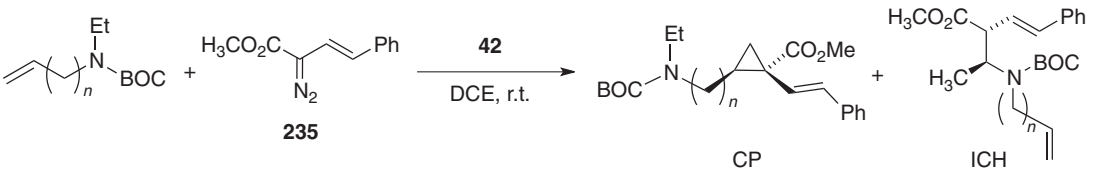


Table 56 Results obtained in the cyclopropanation of alkenylamines with **235**, catalyzed by **42**

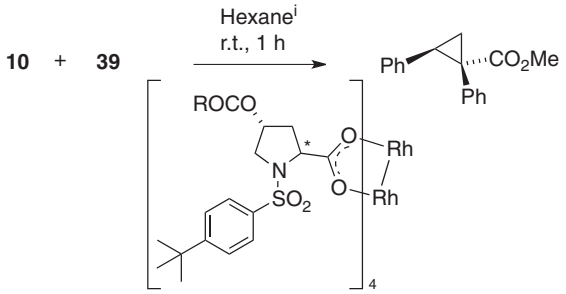


n	de *CP (%)*	ee *CP (%)*	*Yield CP (%)*	*Yield ICH (%)*
1	95	96	64	32
2	98	92	61	30
3	98	95	59	28
4	98	92	55	27

Abbreviation: ICH, intramolecular C–H insertion.

Another modification consisted of using 4-hydroxyproline, instead of proline, which adds a second stereogenic center and allows tuning some other properties, as solubility and steric bulk.[517] In this case, yields and enantioselectivities are similar to those obtained with **42** (Table 57).

Table 57 Results obtained in the cyclopropanation of **10** with **39**, catalyzed by chiral dirhodium tetraprolinates



R	*Absolute configuration C-2*	ee *(%)*	*Yield (%)*
$C_{12}H_{25}$	*S*	84	76
$C_{12}H_{25}$	*R*	90	78
Cyclohexyl	*R*	80	74
Rh_2(*S*-DOSP)$_4$		80	80

Dirhodium tetraprolinates have demonstrated being excellent catalysts for the reactions of vinyl- and aryldiazoacetates with alkenes, but they are not so successful for other diazocompounds. A new family of chiral dirhodium tetracarboxylate catalysts was described by Charette's group by the end of 2000s, which are able to give excellent stereoselectivity results in the reactions with dicarbonyl diazo compounds.[177] The important *trans*-directing effect of the amide group was employed to obtain in most cases a single diastereomer with excellent enantioselectivity (Table 58).

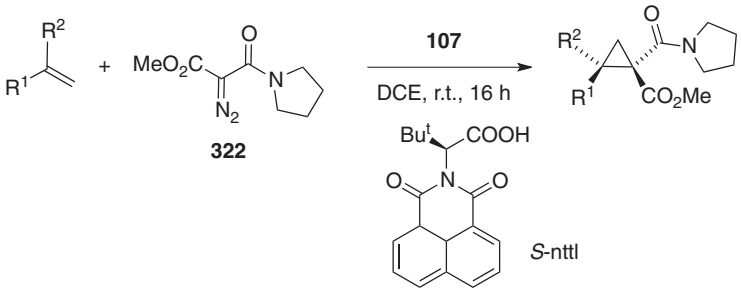
The same group has exploited this system in subsequent works, by using[178,180,199] other diacceptor diazocompounds, as well as Lewis bases as achiral additives. In all cases, excellent diastereo- and enantioselectivities could be obtained, which allow using the highly substituted, chiral cyclopropanes for further synthetic transformations leading to enantiopure α- and β-amino acid derivatives, α-chiral amines, and THFs, among other products (Table 59).

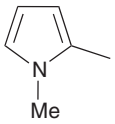
Symmetric diazoesters have also been used as carbenoid precursors, via phenyliodonoium ylides. Although the results are not as good as with other substrates, good enantioselectivities have also been reported.[259,528]

Other diazo compounds bearing donating and accepting groups, like arylcarbonyl diazo compounds and α-alkyl diazoesters, have also been employed with the analogous Rh_2(*S*-PTAD)$_4$ **324** catalyst. Good diastereoselectivities and moderate to good enantioselectivities are obtained with α-phenyl diazoacetone **325** and styrene **10**, as well as with aryl- and vinyldiazoesters.[120] In contrast, Rh_2(DOSP)$_4$ **42** leads to poor enantioselectivities with the former diazocompounds (Table 60).

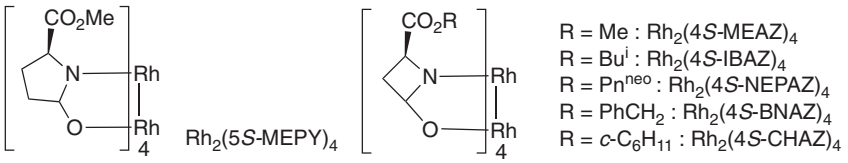
Excellent results have also been reported with α-alkyl diazoesters. Alkyl chain length has a noticeable effect on stereoselectivity, and the best results are obtained when the chain is *n*-propyl or longer (Table 61).[526]

Table 58 Results obtained in the cyclopropanation of alkenes with methyl 2-diazo-3-oxo-3-(pyrrolidin-1-yl)propanoate **322**, catalyzed by $Rh_2(nttl)_4$ **107**



R^1	R^2	dr	ee (%)	Yield (%)
Ph	H	>30:1	96	79
p-$Bu^tC_6H_4$	H	>30:1	96	89
p-FC_6H_4	H	>30:1	97	77
p-ClC_6H_4	H	>30:1	96	81
p-$MeOC_6H_4$	H	>30:1	93	92
p-MeC_6H_4	H	>30:1	96	82
Indene		>30:1	89	63
Ph	Me	>30:1	95	63
1-Naphthyl	H	>30:1	95	86
o-BrC_6H_4	H	>30:1	94	24
(*E*)-PhCH=CH	H	9:1	87	78
BuO	H	9:1	89	70
	H	>30:1	90	31

Compared with carboxylates, dirhodium carboxamidates have been scarcely used with success in intermolecular enantioselective cyclopropanation reactions, in contrast with what happens in the case of intramolecular reactions. One of the first successful examples was published by Doyle and coworkers, who used dirhodium(II) tetrakis[alkyl 2-oxaazetidine-4(*S*)-carboxylates] as catalysts in the cyclopropanation reaction of **10** with alkyl diazoacetates.[846] Only with bulky esters, good enantioselectivities could be achieved in some cases, but with rather low *cis*/*trans*-diastereoselectivities.



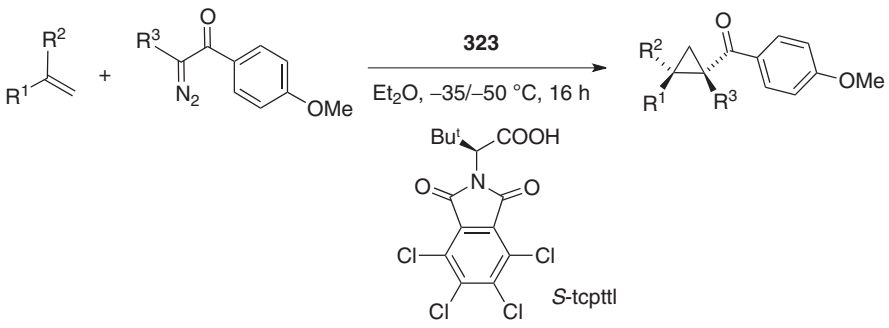
Moderate results were also obtained in the cyclopropanation of 4-methyl-1,3-pentadiene, although these results were improved in a subsequent work, though keeping low diastereoselectivities (Table 62).[847]

Corey and coworkers used a structurally related catalyst, with which good yields and enantioselectivity results were reported for the benchmark cyclopropanation reaction of **10** with **12** (99% *ee* for *cis*-cyclopropanes and 94% *ee* for *trans*-cyclopropanes). 1,1-Diphenylethene **108** also led to good enantioselectivity (92% *ee*).[848]

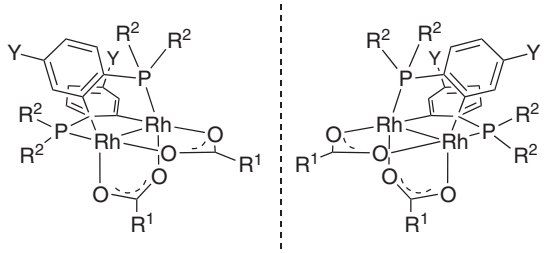
Doyle and coworkers have used these kinds of rhodium catalysts for the preparation of a cyclopropane-configured urea-phenylethylthiazolylthiourea analog that is an human immunodeficiency virus (HIV)-1 reverse-transcriptase inhibitor (Scheme 37).[724]

The last family of chiral rhodium complexes used in intermolecular cyclopropanation reactions is that of dirhodium(II) complexes with bulky *ortho*-metalated aryl phosphines, described by Ubeda and coworkers.[540,541,555,556,727] These phosphine ligands allow tuning the bulkiness of the substituents in the metalated ring, as well as in the aryl groups of the phosphine. Some good enantioselectivity results have been described for the benchmark cyclopropanation reaction, in some cases with good diastereoselectivity as well (up to 90% in *trans*-cyclopropanes with 91% *ee*)[540,727]; but, in general, stereoselectivities are only moderate with these catalysts.

Table 59 Results obtained in the cyclopropanation of alkenes with diacceptor diazo compounds, catalyzed by $Rh_2(tcpttl)_4$ **323**

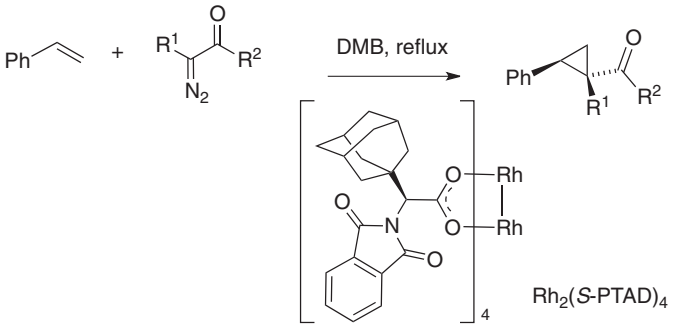


R^1	R^2	R^3	dr	ee *(%)*	*Yield (%)*
Ph	H	NO_2	98:2	93	81
p-MeC_6H_4	H	NO_2	98:2	92	76
p-ClC_6H_4	H	NO_2	98:2	93	91
p-FC_6H_4	H	NO_2	98:2	92	88
p-$O_2NC_6H_4$	H	NO_2	99:1	95	74
p-$F_3CC_6H_4$	H	NO_2	98:2	91	75
m-$MeOC_6H_4$	H	NO_2	97:3	92	85
o-ClC_6H_4	H	NO_2	96:4	92	68
1-Naphthyl	H	NO_2	98:2	95	81
Ph	Me	NO_2	99:1	98	88
Bu^n	H	NO_2	54:46	42	5
Ph	H	CN	95:5	84	92
p-ClC_6H_4	H	CN	97:3	88	94
p-$O_2NC_6H_4$	H	CN	99:1	91	90
m-$MeOC_6H_4$	H	CN	95:5	79	92
o-ClC_6H_4	H	CN	98:2	81	88
1-Naphthyl	H	CN	96:4	73	99
Bu^n	H	CN	81:19	73	75
Ph	Me	CN	84:16	75	97
OBz	H	CN	97:3	94	82
Ph	H	CO_2Me	99:1	88	60
p-ClC_6H_4	H	CO_2Me	99:1	94	31
p-$F_3CC_6H_4$	H	CO_2Me	99:1	93	60
p-$O_2NC_6H_4$	H	CO_2Me	99:1	94	10
p-MeC_6H_4	H	CO_2Me	99:1	84	70
o-ClC_6H_4	H	CO_2Me	>97:3	90	33
1-Naphthyl	H	CO_2Me	99:1	85	52



Apart from dirhodium catalyst, a couple of examples have been described of single metal rodhium complexes leading to moderate enantioselectivities in the benchmark cyclopropanation reaction. The first one is a chiral bis(pyrazolyl)pyridine–Rh(III) complex, with with enantioselectivities of 80–85% *ee* could be obtained, but with almost no *cis*/*trans*-diastereoselectivity.[378] The second one is a chiral bisoxazoline–Rh(II) complex, which led up to 84% *ee* with low *cis*/*trans*-selectivity (approxiamtely 60:40).[546]

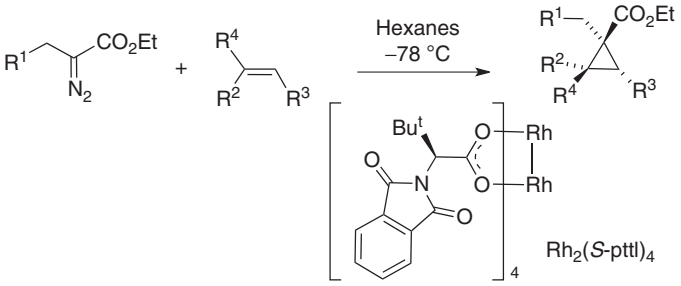
Table 60 Results obtained in the cyclopropanation of styrene with α-aryl diazoketones, catalyzed by Rh_2(*S*-PTAD)$_4$ **42**



42

R^1	R^2	dr	ee *(%)*	*Yield (%)*
Ph	Me	>95:5	85	92
(*E*)-PhCH=CH	Me	>95:5	54	85
p-BrC_6H_4	Me	>95:5	89	93
p-$O_2NC_6H_4$	Me	>95:5	88	82
Ph	Et	>95:5	85	95
Ph	Pr^n	>95:5	91	92
Ph	Bu^i	>95:5	94	82
Ph	Ph	>95:5	51	91
p-ClC_6H_4	$Bu^tCH_2CH_2$	>95:5	93	93
p-ClC_6H_4	Bu^n–≡	>95:5	95	95
p-ClC_6H_4	TMS–≡	>95:5	98	98
p-ClC_6H_4	Bu^t–≡	>95:5	95	95

Table 61 Results obtained in the cyclopropanation of alkenes with α-alkyl ethyl diazoacetate, catalyzed by Rh_2(*S*-pttl)$_4$ **326**



326

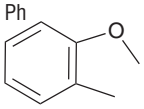
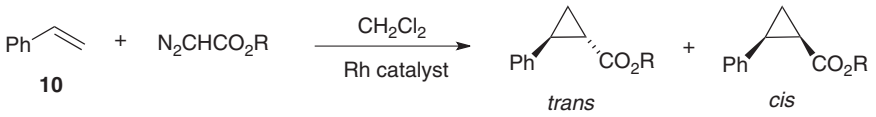
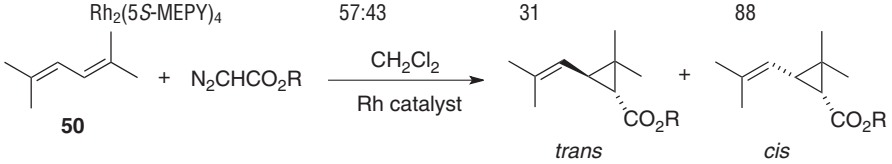
R^1	R^2	R^3	R^4	dr	ee *(%)*	*Yield (%)*
Me	Ph	H	H	91:9	3	68
Et	Ph	H	H	92:8	79	76
Pr^n	Ph	H	H	>95:5	94	85
Bu^n	Ph	H	H	>95:5	96	84
Pn^i	Ph	H	H	>95:5	99	89
Bu^n	*p*-$MeOC_6H_4$	H	H	>95:5	89	84
Bu^n	*p*-FC_6H_4	H	H	>95:5	97	100
Bu^n	PhCH=CH	H	H	>95:5	85	72
Pr^n	1-Naphthyl	H	H	>95:5	93	77
Bu^n	Ph	H	Me	>95:5	97	89
Bu^n	Ph	H	Ph	–	61	93
Pn^i		H	>95:5	99	94	

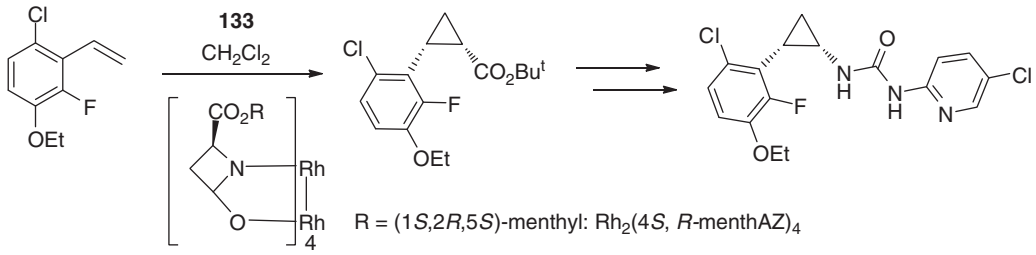
Table 62 Results obtained in the cyclopropanation of alkenes with alkyl diazoacetates, catalyzed by dirhodium carboxamidates



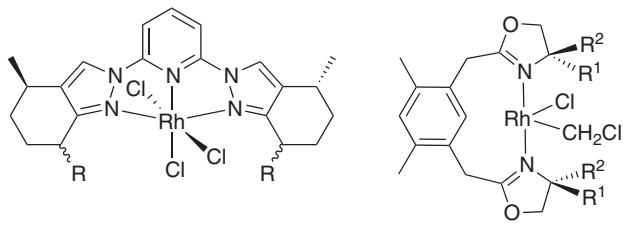
R	*Catalyst*	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Et	Rh_2(4*S*-BNAZ)$_4$	41:59	23	29	74
Et	Rh_2(4*S*-IBAZ)$_4$	36:64	47	73	62
Et	Rh_2(5*S*-MEPY)$_4$	56:44	58	33	59
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-BNAZ)$_4$	41:59	48	68	74
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-IBAZ)$_4$	34:66	77	95	74
(*c*-C_6H_{11})$_2$CH	Rh_2(5*S*-MEPY)$_4$	58:42	53	91	69
(1*R*,2*S*,5*R*)-menthyl	Rh_2(4*S*-BNAZ)$_4$	43:57	24	44	85
(1*R*,2*S*,5*R*)-menthyl	Rh_2(4*S*-IBAZ)$_4$	38:62	62	88	56
(1*R*,2*S*,5*R*)-menthyl	Rh_2(5*S*-MEPY)$_4$	52:48	38	80	34
(1*S*,2*R*,5*S*)-menthyl	Rh_2(4*S*-IBAZ)$_4$	44:56	62	92	61
(1*S*,2*R*,5*S*)-menthyl	Rh_2(5*S*-MEPY)$_4$	57:43	31	88	74



(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-IBAZ)$_4$	54:46	>98	66	81
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-BNAZ)$_4$	42:58	>98	70	89
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-MEAZ)$_4$	43:57	91	63	86
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-NEPAZ)$_4$	49:51	>98	70	91
(*c*-C_6H_{11})$_2$CH	Rh_2(4*S*-CHAZ)$_4$	53:47	83	60	80



Scheme 37

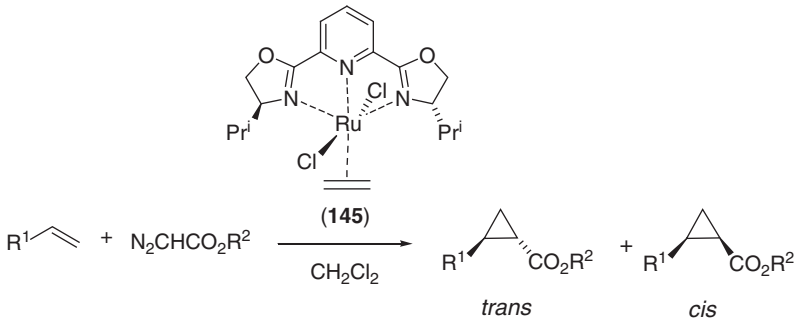


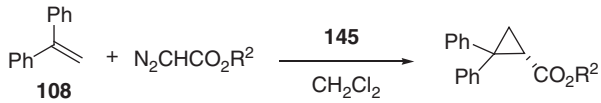
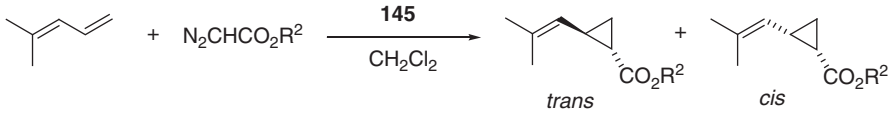
4.20.4.1.5.2.3 Ruthenium catalysts

The first efficient enantioselective cyclopropanation catalysts with ruthenium were described by Nishiyama and coworkers, who used the chiral bis(oxazolinyl)pyridine–Ru(II) (pybox–Ru(II)) complex **145**,[136,138,588] above all that bearing isopropyl groups in the oxazoline rings (**Table 63**).

A revision about the use of chiral pybox–Ru(II) complexes in enantioselective cyclopropanation reactions has been published by Nishiyama.[563] Several modifications to the pybox structure, by introducing hydroxyl groups, have been described to allow

Table 63 Results obtained in the cyclopropanation of alkenes with alkyl diazoacetates, catalyzed by **145**



R^1	R^2	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	Me	90:10	88	70	74
Ph	Et	91:9	89	79	73
Ph	Bu^t	97:3	94	87	65
Ph	(1*S*,2*R*,5*S*)-menthyl	97:3	87	97	82
Ph	(1*R*,2*S*,5*R*)-menthyl	97:3	96	80	83
p-ClC_6H_4	(1*R*,2*S*,5*R*)-menthyl	96:4	95	83	84
p-$MeOC_6H_4$	(1*R*,2*S*,5*R*)-menthyl	95:5	97	n.d.	96
$PhCH_2$	(1*R*,2*S*,5*R*)-menthyl	93:7	97	n.d.	45
Pn^n	(1*R*,2*S*,5*R*)-menthyl	92:8	98	94	54
	 **108**				
–	(1*R*,2*S*,5*R*)-menthyl	–	65	–	55
–	(1*S*,2*R*,5*S*)-menthyl	–	89	–	55
	 *trans* *cis*				
–	(1*R*,2*S*,5*R*)-menthyl	79:21	>98	79	86

using these catalysts in protic media.[563] However, Wurz and Charette have shown that even the original Nishiyama's catalyst can be used in aqueous medium with results similar to those obtained in organic solvents.[489]

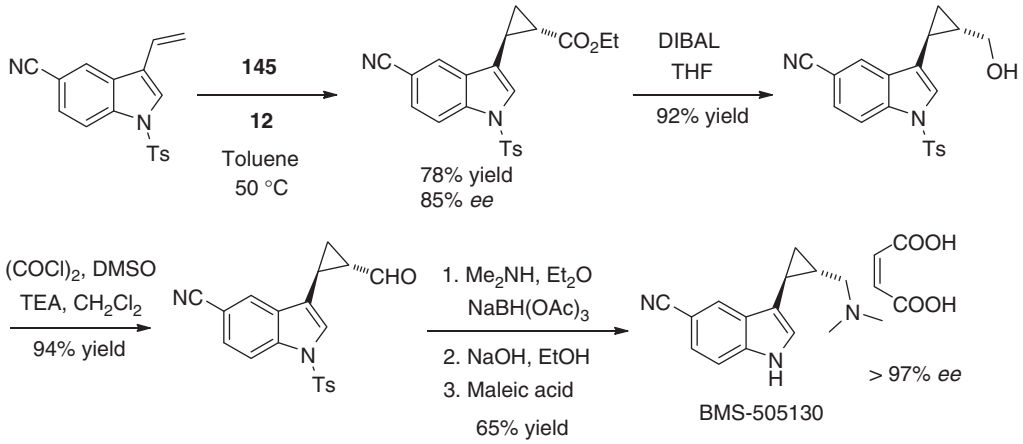
An interesting question raised by Nishiyama was the efficiency of the so-called 'single-chiral' pybox ligands (i.e., ligands without C_2-symmetry). With the *tert*-butyl-substituted C_1-symmetric ligand, up to 90% *ee* could be obtained in the benchmark cyclopropanation of **10** with **12**.[849] An explanation for this unexpected result was given by García and coworkers, based on a computational study.[717] Martínez-Merino and coworkers have described some efficient immobilization strategies for Nishiyama's catalyst, leading to good enantioselectivities in several catalyst reuses.[595–597]

Some synthetic applications of Nishiyama's catalysts have been described. Marcin et al. have used the catalytic enantioselective cyclopropanation of 1-tosyl-3-vinylindoles for the synthesis of conformationally restricted homotryptamines, including the selective serotonin reuptake inhibitor BMS-505130 (**Scheme 38**).[591]

Similarly, Chen and coworkers have described the process development of the multikilogram-scale synthesis of the same selective serotonin reuptake inhibitor,[592] also using the pybox–Ru(II)-catalyzed cyclopropanation as the key step to obtain the stereogenic centers of the right configuration. An overall yield of 34% after 13 chemicals steps and nine isolations was obtained.

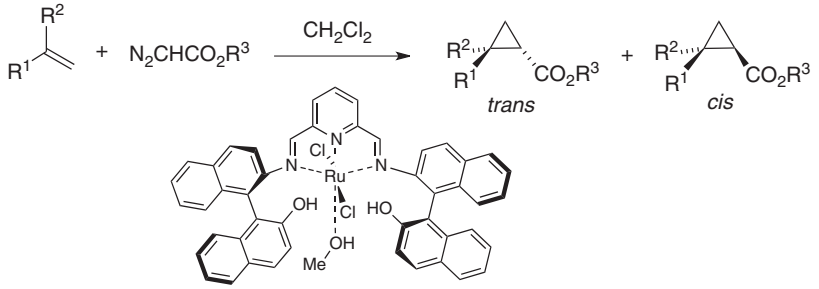
After the efficient pybox–Ru(II) catalysts, other structurally related ruthenium complexes have been described and tested in asymmetric cyclopropanation reactions. For instance, Zhang and coworkers described an *N*,*O*-mixed polydentate ligand bearing a pyridylbisimine moiety (**327**).[129] Good *trans*-selectivities with moderate to good enantioselectivities were obtained in the cyclopropanation of **10** with alkyl diazoacetates, and these good results could also be extended to other alkenes (**Table 64**).

The bis(tiazolidyl)pyridines described by Simmoneaux and coworkers are also related with the original pybox ligands[599] although the enantioselectivity results obtained were inferior. The chiral bis(oxazolinyl)thiophenes described by Zingaro and coworkers are also structurally related.[850] In this case, good enantioselectivitites were obtained in the cyclopropanation reaction of 1,1-diphenylethene **108** with **12**, catalyzed by the ruthenium complexes of these ligands (up to 99% *ee* with 85% yield in dichloromethane at room temperature).

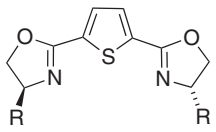


Scheme 38

Table 64 Results obtained in the cyclopropanation of alkenes with alkyl diazoacetates, catalyzed by the **327**–$RuCl_2$ complex



R^1	R^2	R^3	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	H	Me	85:15	88	56	85
Ph	H	Et	90:10	96	83	88
Ph	H	Pr^i	95:5	90	63	88
Ph	H	Bu^t	97:3	86	54	75
Ph	H	(1*R*,2*S*,5*R*)-menthyl	95:5	58	44	66
Ph	H	(1*S*,2*R*,5*S*)-menthyl	96:4	85	4	76
p-ClC_6H_4	H	Et	90:10	92	70	45
p-$MeOC_6H_4$	H	Et	87:13	86	69	78
2-Naphthyl	H	Et	90:10	83	72	78
Pn^n	H	Et	83:17	91	86	45
Ph	Me	Et	47:53	91	93	82

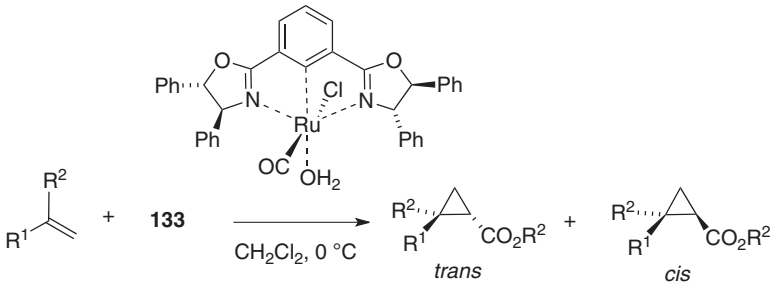


R = Et, Pr^i, $PhCH_2$, Bu^t

Nishiyama and coworkers have also described a variant of the pybox ligand in which the pyridine ring is substituted by benzene, leading to the so-called phebox ligands. The Ru(II) complexes of these ligands have also been employed in enantioselective cyclopropanation reactions with excellent yields, *trans*-selectivities and enantioselectivities (Table 65).[600]

A C_1-symmetric variant of the phebox ligand has been used by Iwasa and coworkers to prepare an Ru(II) catalyst (**328**) with which excellent stereoselectivities have been obtained in cyclopropanation reactions of succinimidyl diazoacetate **70** with a number of alkenes (Table 66).[145]

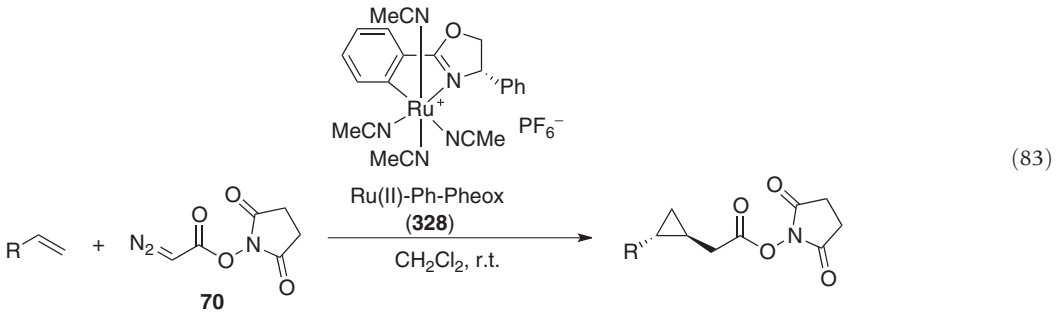
Table 65 Results obtained in the cyclopropanation of alkenes with **133**, catalyzed by the **143**–RuClCO complex



R^1	R^2	trans:cis	ee trans *(%)*	*Yield (%)*
Ph	H	92:8	98	90
p-$MeOC_6H_4$	H	92:8	99	87
p-MeC_6H_4	H	94:6	99	88
p-ClC_6H_4	H	95:5	99	92
p-BrC_6H_4	H	96:4	98	89
p-$F_3CC_6H_4$	H	96:4	99	85
o-ClC_6H_4	H	95:5	98	87
m-ClC_6H_4	H	92:8	98	86
2-Naphthyl	H	93:7	99	88
PhCH=CH	H	82:18	98	91
Ph	Me	35:65	93	80
$PhCH_2CH_2$	H	92:8	87	59

Table 66 Results of the reactions between **70** and different alkenes in the presence of **328** (equation 83)

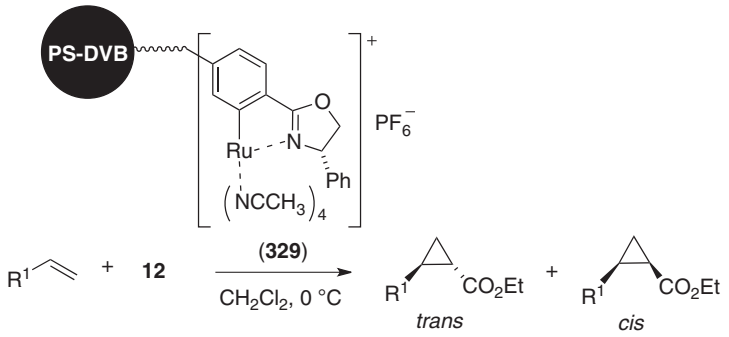
R	*Yield (%)*	trans/cis	% ee
Ph	98	>99:1	95
4-MeC_6H_4	95	>99:1	99
3-MeC_6H_4	97	>99:1	91
2-MeC_6H_4	92	>99:1	91
4-$MeOC_6H_4$	98	>99:1	92
4-ClC_6H_4	92	>99:1	99
9-Carbazolyl	99	>99:1	98
BuO	94	>99:1	99
^{i}BuO	94	>99:1	99

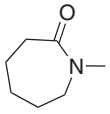
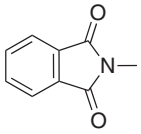
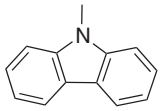


(83)

A macroporous-polymer-supported chiral Ru(II)–phenyloxazoline catalyst **329**,[601] has been prepared through immobilization of the above mentioned catalysts, and has been efficiently used in a variety of heterogeneously catalyzed asymmetric intermolecular cyclopropanation reactions with high reusability (Table 67; Figure 7).

Table 67 Results obtained in the cyclopropanation of alkenes with **12**, catalyzed by **329**



R^1	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	89:11	98	71	99
p-$MeOC_6H_4$	94:06	98	53	93
p-MeC_6H_4	94:06	98	96	91
p-ClC_6H_4	94:06	98	28	>99
	88:12	96	99	96
	99:01	94	n.d.	94
	92:08	97	55	90
	99:01	>99	n.d.	96
MeCONH	70:30	91	91	96
Bu^tO	76:24	96	86	90
Bu^iO	90:10	96	92	98
Bu^nO	80:20	91	62	99
MeCOO	90:10	97	95	80

Ruthenium porphyrin complexes have also been employed as catalysts for enantioselective cyclopropanation reactions. As the porphyrin ligand provides a symmetric square-planar environment to the metal atom, chiral bulky substituents are required to obtain good selectivities. Thus, Che and coworkers described good *trans*-selectivities with moderate to good enantioselectivities in the reactions of ethyl diazoacetate with different styrenes, catalyzed by an Ru(II)–porphyrin complex **330** (Table 68).[92,93,603]

As in the case of pybox ligands, immobilization strategies have been described for these ruthenium porphyrin complexes, leading to chiral heterogeneous catalysts.[612] For instance, the copolymerization of a vinylporphyrin with cross-linking monomers leads to porous polymers that can be used in several reactions with moderate enantioselectivities.[613]

Chiral salen–ruthenium complexes have been used by Katsuki and coworkers as catalysts in the enantioselective cyclopropanation reaction of **10** and other alkenes with *tert*-butyl diazoacetate **133**.[618,851,852] In this case, good *cis*-selectivity and enantioselectivity in the *cis*-cyclopropanes were obtained (Table 69).

Immobilized salen–Ru(II) complexes have also been prepared and successfully tested as recoverable catalysts for the reaction between **10** and **12**.[623]

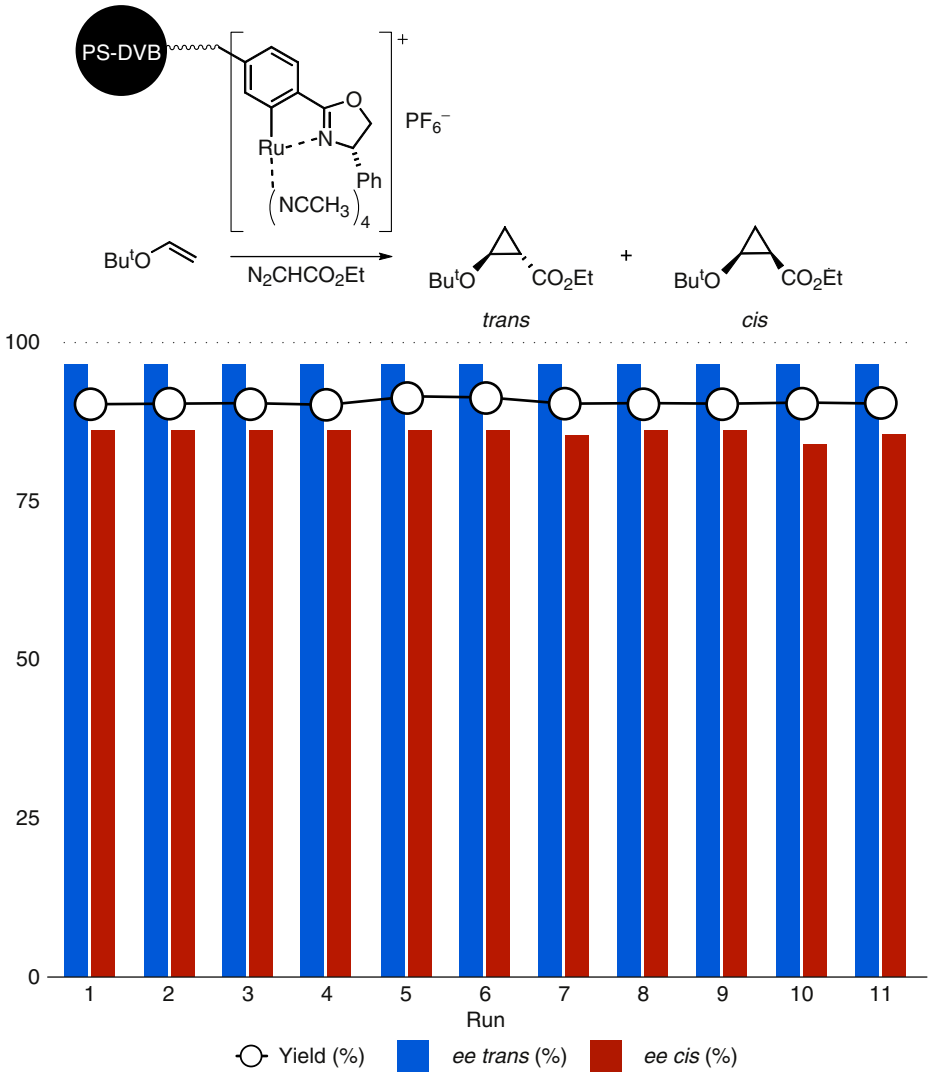


Figure 7 High recoverability of a macroporous-polymer-supported chiral Ru(II)–phenyloxazoline catalyst in a cyclopropanation reaction.

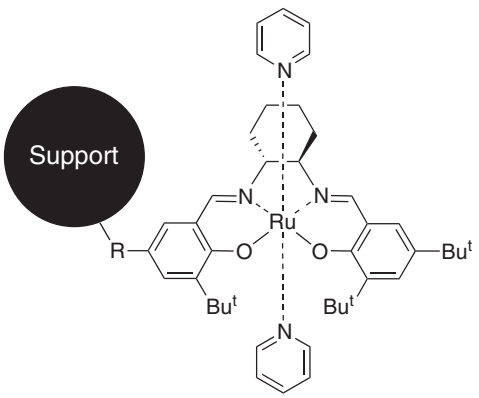
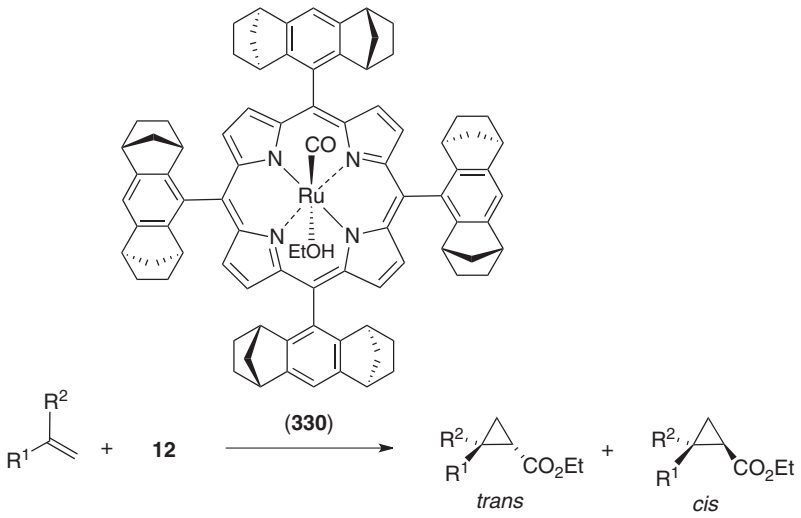
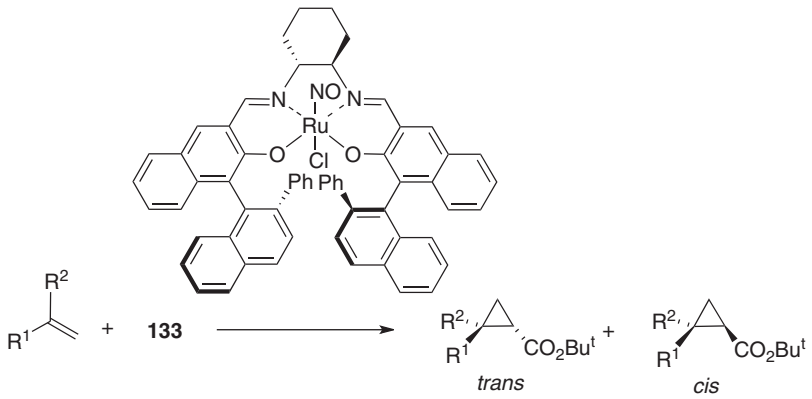


Table 68 Results obtained in the cyclopropanation of styrenes with **12**, catalyzed by **330**



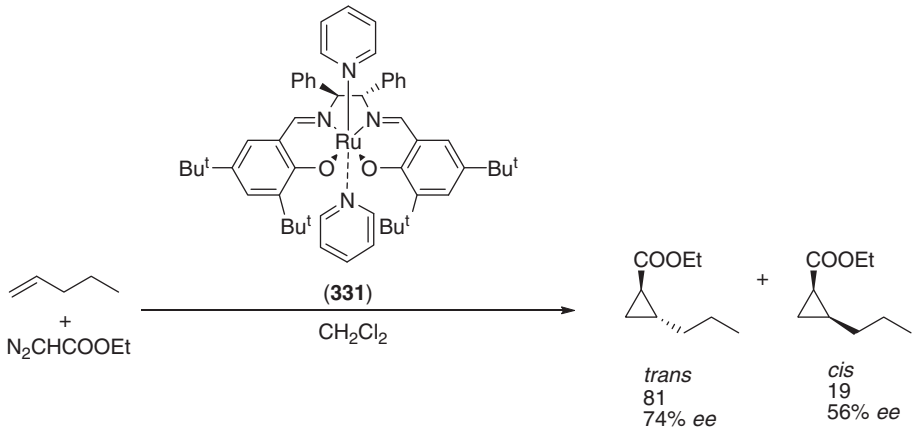
R^1	R^2	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	H	95:5	87	4	83
Ph	Me	75:25	87	35	69
Ph	Ph	–	81		76
p-ClC_6H_4	H	96:4	90	4	66
p-MeC_6H_4	H	95:5	81	9	78
p-$MeOC_6H_4$	H	94:6	85	8	61

Table 69 Results obtained in the cyclopropanation of styrenes with **133**, catalyzed by a chiral salen–ruthenium complex



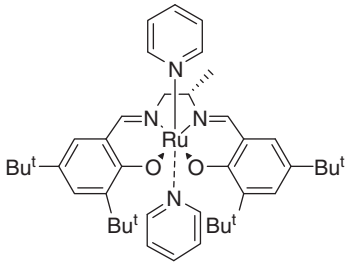
R^1	R^2	trans:cis	ee trans *(%)*	ee cis *(%)*	*Yield (%)*
Ph	H	7:93	2	98	36
p-ClC_6H_4	H	7:93	–	95	44
p-$MeOC_6H_4$	H	6:94	5	96	62
Ph	Me	20:80	–	97	74

Good diastereo- and enantioselectivities have been achieved in the cyclopropanation of 1-pentene with ethyl diazoacetate **12** by means of the chiral Ru–salen complex **331** (equation 84). The low (20%) initial yield of this reaction (due to an extensive carbene dimerization) has been improved by successive addition of ethyl diazoacetate (**12**).[619]



(84)

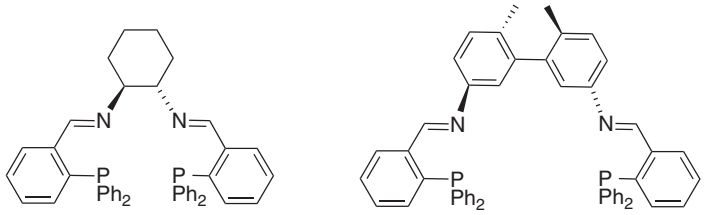
Ruthenium catalysts have also been successfully used in the cyclopropanation of electron-deficient alkenes. Thus, excellent results (95% yield, *trans*/*cis* = 100:1, 95% *ee*) were obtained for the reaction of methyl methacrylate **25** with ethyl diazoacetate **12** in the presence of the chiral Ru complex **332**.[619]



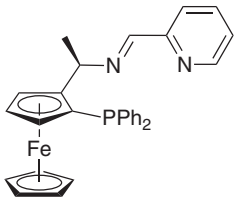
332

The application of a number of Ru catalysts to the cyclopropanation of acrylonitrile **281** with ethyl diazoacetate **12** showed a variety of results depending on the catalyst.[619] Thus, the highest yield was obtained for **332**, though leading to low stereoselectivities. Instead, the good enantioselectivities obtained for **331** contrasted with the low yield (28%) and *trans*/*cis* ratio (1.2:1).

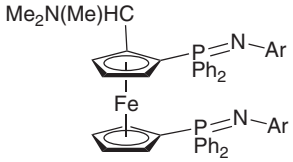
Structurally related to the salen ligands are the PNNP chiral ligands used by Zheng and coworkers[853] and by Bachmann and Mezzetti[94] in the benchmark cyclopropanation reaction. These ligands exhibit *cis*-selectivity to some extent, and a wide range of enantioselectivities, depending on the additive used.



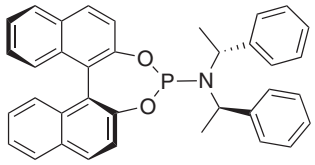
Better results have been described with other NNP and NP ligands. For instance, Zheng and coworkers have described a ferrocenephosphineimine ligand with which up to 95% in *cis*-cyclopropanes and 90% in *trans*-cyclopropanes could be obtained in the reaction of **10** with**12**. Use of bulkier diazoesters allowed increasing *trans*-selectivity up to 97%, but at the cost of lower enantioselectivities (62% *ee*).[630]

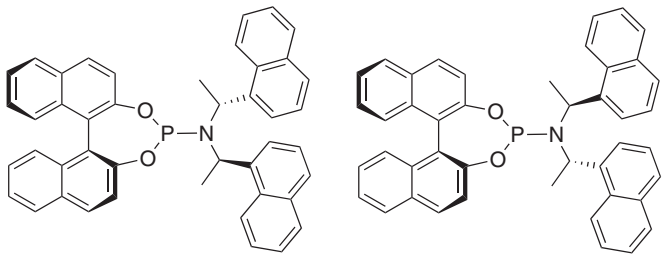


Kim and coworkers described the use of chiral (iminophosphoranyl)ferrocenes, which are able to achieve high diastereoselectivity (up to 95% in *cis*-cyclopropanes and 97% in *trans*-cyclopropanes, depending on the substrate) as well as enantioselectivity (up to 99% *ee*) in Ru-catalyzed asymmetric cyclopropanation of various alkenes with **112**.[628]



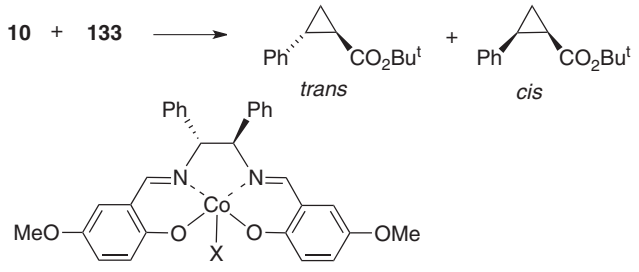
Chiral ruthenium–phosphoramidite complexes have also been tested in the benchmark cyclopropanation reaction, but only moderate enantioselectivities with low diastereoselectivities have been obtained in the best cases.[582]





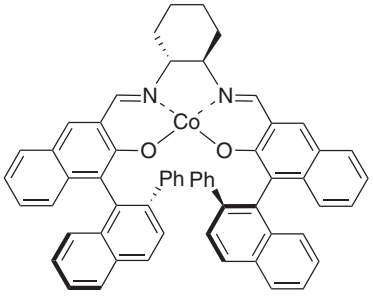
4.20.4.1.5.2.4 Cobalt and iridium catalysts

There are few examples of asymmetric cyclopropanation reactions catalyzed by chiral cobalt complexes leading to good enantioselectivities. One of the first examples was described by Katsuki, using chiral Co(III)–salen and Co(II)–salen complexes.[618,852] Depending on the salen ligand employed, high *trans*- or *cis*-diastereoselectivity was obtained, keeping good enantioselectivities in both cyclopropanes. In the best case, 90% yield with 98% *cis*-selectivity and 98% *ee* could be obtained in the reaction of **10** with *tert*-butyl diazoacetate **133**.

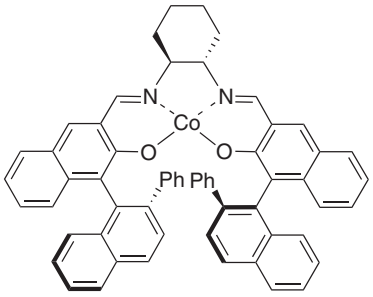


80% yield, 96:4 *trans:cis*, 93% *ee* (*trans*)

(85)



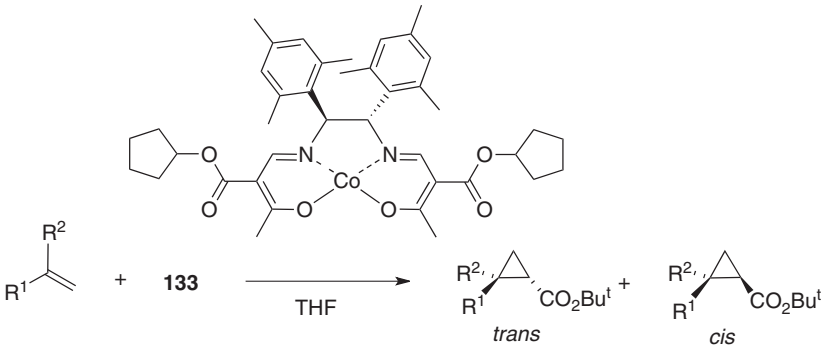
90% yield, 2:98 *trans:cis*, 98% *ee* (*cis*)



17% yield, 3:97 *trans:cis*, –99% *ee* (*cis*)

Structurally related to salen are the 3-oxobutylideneaminato ligands. With a Co(II) complex of one of these ligands, Yamada et al. have described excellent enantioselectivity results in the cyclopropanation reactions of several alkenes with **133** (Table 70).[854]

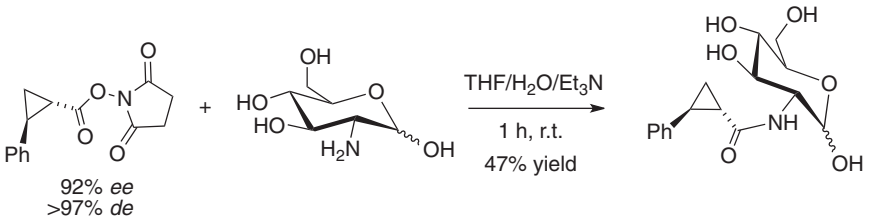
Table 70 Results obtained in the cyclopropanation of styrenes with **133**, catalyzed by a chiral 3-oxobutylideneaminato–Co(II) complex



R^1	R^2	trans:cis	ee trans *(%)*	*Yield (%)*
Ph	H	90:10	96	97
2-Naphthyl	H	87:14	96	95
Ph	Me	46:53	99	47
Ph	Ph	–	90	99

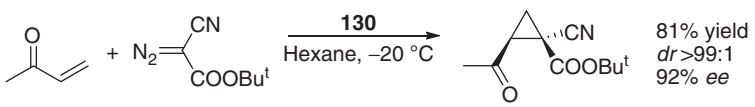
More recently, Zhang and coworkers have described a chiral Co(II)–porphyrin catalyst (**130**) able to provide excellent results in the cyclopropanation reaction of various alkenes with succinimidyl diazoacetate **70**.[143] Complete *trans*-selectivity with high enantioselectivities were obtained in all cases (Table 71).

Owing to the mild and neutral reaction conditions, the postderivatization approach was able to tolerate a number of different functional groups, so this catalyst could be used for synthetic applications, for instance, the synthesis of multifunctional cyclopropyl amides from chiral α-amino acids or β-amino alcohols, or the preparation of the cyclopropyl carboxamide of an amino sugar.



(86)

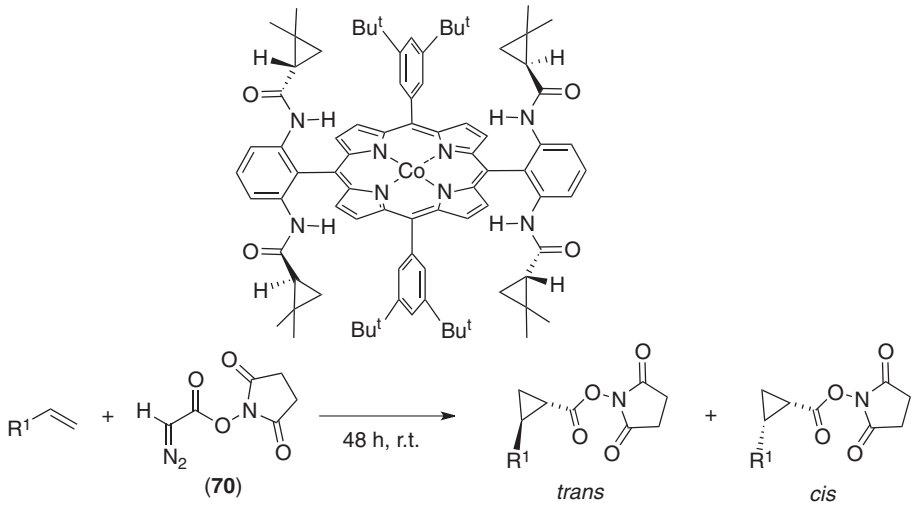
Cobalt catalysts (**53**) have also been successfully used in the cyclopropanation of electron-deficient alkenes with *tert*-butyl cyanodiazoacetate **205**. Thus, highly stereoselective cyclopropanation reactions have been achieved with butenone (**271** 81% yield, *trans*/*cis* >99:1, 92% *ee*) (equation 87), methyl acrylate (**333** 90% yield, *trans*/*cis* >99:1, 88% *ee*), ethyl acrylate (**334** 79% yield, *trans*/*cis* >99:1, 92% *ee*), acrylonitrile (**281** 99% yield, *trans*/*cis*=72:28, 82% *ee*), acrylamide (**335** 72% yield, *trans*/*cis* >99:1, 82% *ee*), and *N*,*N*-dimethylacrylamide (**336** 99% yield, *trans*/*cis* >99:1, 87% *ee*).[194]



(87)

Katsuki and coworkers have also described a salen-iridium catalyst, able to provide excellent results in the construction of α-spirocyclopropyl lactones through asymmetric cyclopropanation reactions using the vinyl diazolactone 3-diazo-3,6-dihydro-2*H*-pyran-2-one **95** as the carbonyl carbene source.[216] Under optimized conditions, excellent yields, diastereo- and enantioselectivity results were obtained for a variety of alkenes. Subsequent hydrolysis and Cope rearrangement of the products led to the corresponding 1,4-cycloheptadiene derivatives in a stereospecific way (Table 72).

Table 71 Results obtained in the cyclopropanation of alkenes with **70**, catalyzed by a chiral Co(II)–porphyrin complex



R^1	trans:cis	ee trans *(%)*	*Yield (%)*
Ph	>99:1	92	86
p-MeC_6H_4	>99:1	95	90
p-$Bu^tC_6H_4$	>99:1	97	80
p-$MeOC_6H_4$	>99:1	95	71
p-ClC_6H_4	>99:1	90	66
p-$F_3CC_6H_4$	>99:1	90	77
p-$AcOC_6H_4$	>99:1	91	71
m-$O_2NC_6H_4$	>99:1	92	50
2-Naphthyl	99:1	91	33
EtOOC	>99:1	89	57
Me_2NOC	>99:1	96	52
MeOC	>99:1	91	55

4.20.4.1.6 Applications of cyclopropanation reactions to total synthesis

A review on the synthesis of cyclopropane-containing natural products has been published.[855] A number of total syntheses involving intermolecular cyclopropanation reactions have been reported.

4.20.4.1.6.1 (±)-Dysibetaine CPa

The cyclopropanation reaction between a sulfonium ylide and an electron-deficient olefin was used to build the ring of dysibetaine CPa **337**, an amino acid isolated from the marine sponge *Lendefeldia chondroids*.[856,857] Thus, the reaction of *p*-nitrophenylmaleimide **338** with the ethyl acetate thianium ylide afforded a two enantiomer pairs of cyclopropanes in 74% yield, the minor pair being subsequently used for the total synthesis of racemic dysibetaine CPa **337** (Scheme 39).

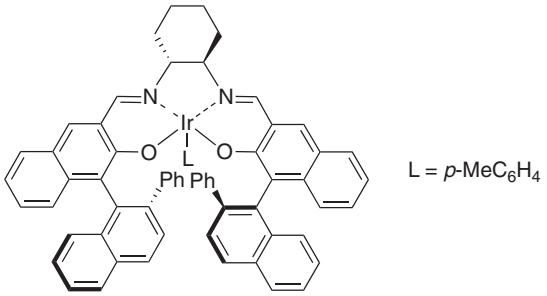
4.20.4.1.6.2 Cilastatin

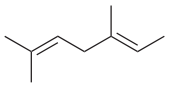
A nonstereoselective total synthesis of cilastatin **339**, a renal dipeptidase inhibitor, has been published by Vinogradov et al.[858] In that work, 2-methylpropene **89** and methyl diazoacetate **54** react to afford racemic methyl 2,2-dimethylcyclopropanecarboxylate using $Rh_2(OAc)_4$ **36** as a catalyst (Scheme 40). Such reaction mixture was used for obtaining a mixture containing cilastatin **339** as well as an epimer.

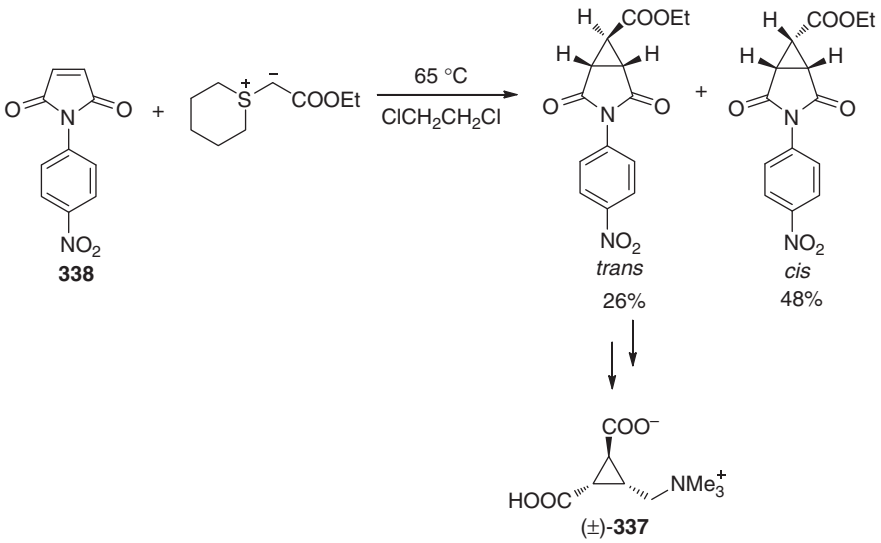
4.20.4.1.6.3 (+)-Grenadamide

A *trans*-selective cyclopropanation reaction was used by Minuth and Boysen in the total synthesis of (+)-grenadamide **340**, a lipid occurring in the marine cyanobacteria *Lyngbya majuscula* living in Grenada in the Southern Caribbean (Scheme 41).[859] In this case, the reaction of 1-nonene **341** with ethyl diazoacetate **12** catalyzed by 3-*O*-formyl-glucoBox **342** yielded a large amount of the desired *trans*-cyclopropane product (75% yield, 73% *trans*, 90% *ee trans*, hence 52% yield of the desired product), though the major enantiomer showed a stereochemistry reverse to that of the natural product. Several further steps were required for the total synthesis of nonnatural (+)-grenadamide **340**.

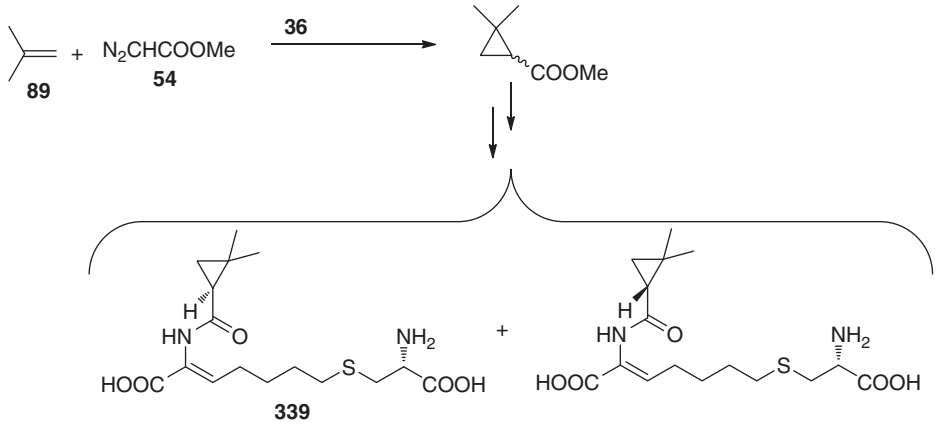
Table 72 Results obtained in the cyclopropanation of alkenes with **95**, catalyzed by a chiral Ir(III)–salen complex



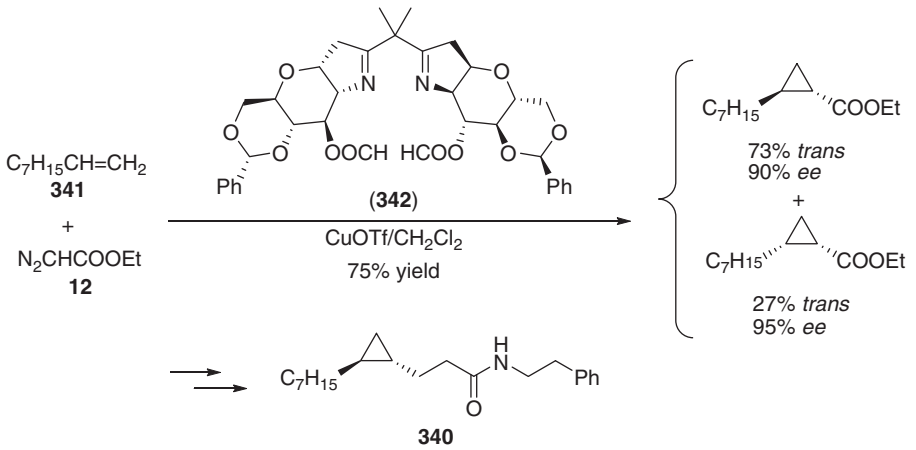
R^1	trans:cis	ee trans *(%)*	*Yield (%)*
p-$MeOC_6H_4$	>99:1	97	99
p-ClC_6H_4	>99:1	99	99
p-BrC_6H_4	>99:1	99	92
p-FC_6H_4	>99:1	99	94
p-MeC_6H_4	>99:1	99	99
o-$MeOC_6H_4$	>99:1	99	96
m-$MeOC_6H_4$	>99:1	98	93
m-$O2NC_6H_4$	86:14	99	86
o-ClC_6H_4	94:6	98	87
m-ClC_6H_4	>99:1	99	67
2-Naphthyl	82:18	99	99
Ph	>99:1	98	99
(*E*)-PhCH=CH	>99:1	98	98
(*E*)-PhC(Me)=CH	95:5	99	79
	>99:1	99	92
	>99:1	98	97



Scheme 39



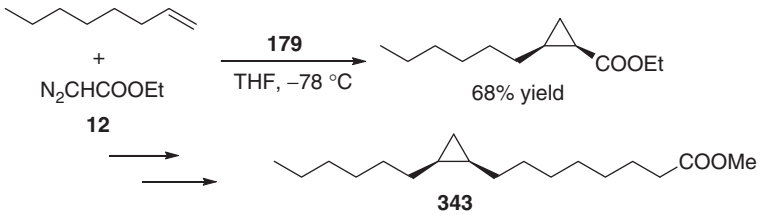
Scheme 40



Scheme 41

4.20.4.1.6.4 Methyl 8-[(1R,2S)-2-hexylcyclopropyl]-octanoate

Two strategies have been employed for the *cis*-selective formation of cyclopropane ring in the total syntheses of cyclopropane fatty acid derivatives. A *cis*-selective cyclopropanation reaction has been developped by Katsuki and coworkers in the enantioselective synthesis of methyl 8-[(1*R*,2*S*)-2-hexylcyclopropyl]-octanoate **343**, a lipid occurring in the membrane of *Escherichia coli* B-ATCC 11303. In the first step of that work, 1-octene **28** was reacted with ethyl diazoacetate **12** in the presence of the Ir–salen complex **179** to yield a reaction mixture with the desired stereochemistry (68% yield, *trans*/*cis* = 2:98, 98% *ee*) (Scheme 42).[649]

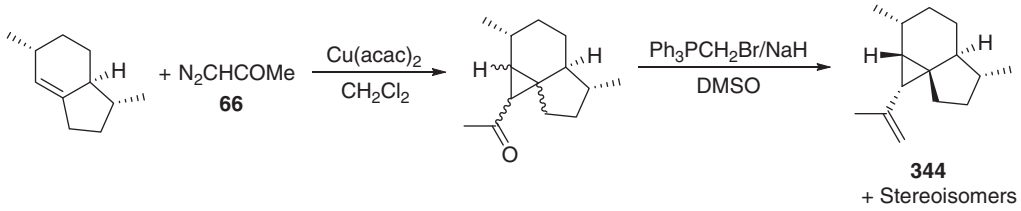


Scheme 42

4.20.4.1.6.5 (+)-Tamariscene

The Paul–König total synthesis of (+)-tamariscene **344**, a sesquiterpenoid obtained from the angiosperm *Valeriana officinalis*, involves the reaction of a bicycloalkene with diazoacetone **66** in the presence of $Cu(acac)_2$ **110** to yield a mixture of four

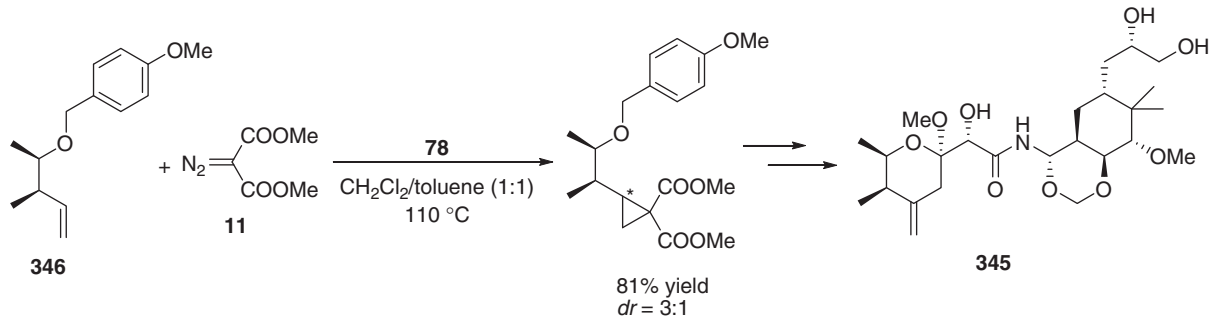
stereoisomers (Scheme 43).[860] The subsequent Wittig reaction with a methylene synthetic equivalent afforded a new diastereomeric mixture, from which the desired product could be isolated by preparative GC.



Scheme 43

4.20.4.1.6.6 Mycalamide A

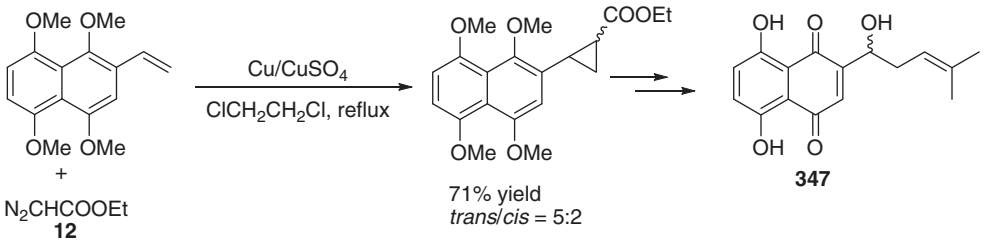
Mycalamide A **345** is a natural product obtained from the marine sponge *Mycale* sp., which blocks T-cell activation and exhibits immunosuppressive activity. The total synthesis of Mycalamide A carried out by Toyota and coworkers involves the reaction between the chiral olefin **346** and dimethyl diazomalonate **11** catalyzed by CuOTf **78**, which generates the corresponding cyclopropane diastereomixture with 81% yield (Scheme 44).[861]



Scheme 44

4.20.4.1.6.7 (±)-Shikalkin

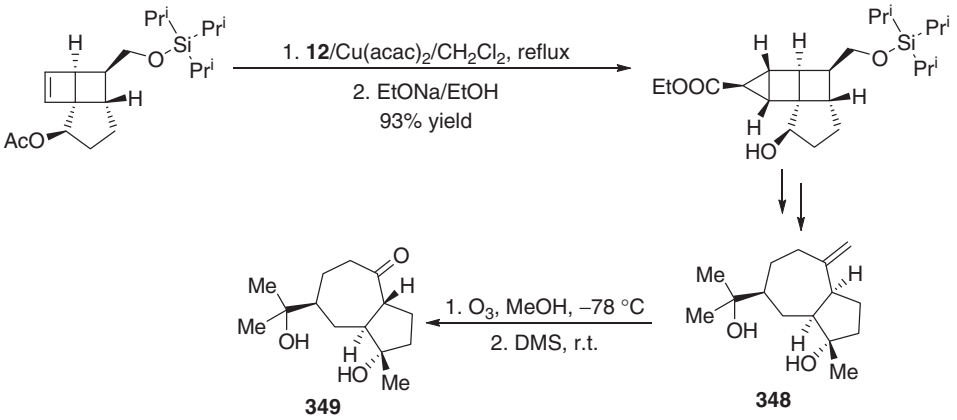
Shikalkin **347** is a naturally occurring enantiomer mixture obtained from the roots of *Lithospermum erythrorhizon* exhibiting antiinflammatory, antibacterial, antifungal, immunostimulating, and antitumor activities. The total synthesis of shikalkin by Novikov et al. includes the reaction between a vinylnaphthalene derivative and ethyl diazoacetate **12** catalyzed by $Cu/CuSO_4$ (Scheme 45).[862]



Scheme 45

4.20.4.1.6.8 Pleocarpenene and pleocarpenone

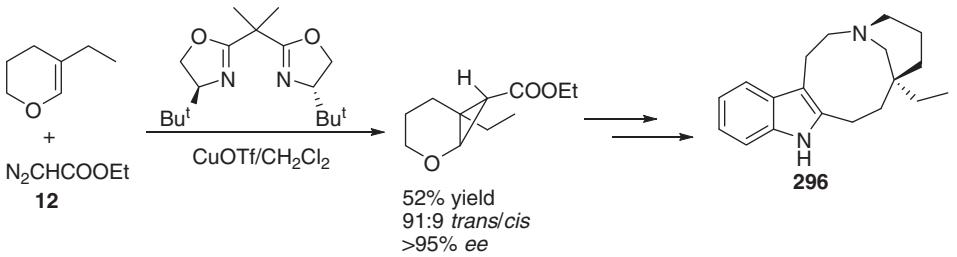
Pleocarpenene **348** and pleocarpenone **349** are two guaiane natural products obtained from the small shrub *Pleocarphus revolutus*. Cyclopropanation of a polycyclic alkene was conceived as a major key in the total synthesis of these compounds by Snapper and coworkers.[863] Interestingly, a one-pot cyclopropanation/deacetylation was carried out with high efficiency (93% yield). Several further steps afforded pleocarpenene **348**, which was ozonized and epimerized to afford pleocarpenone **349** (Scheme 46).



Scheme 46

4.20.4.1.6.9 (+)-Quebrachamine

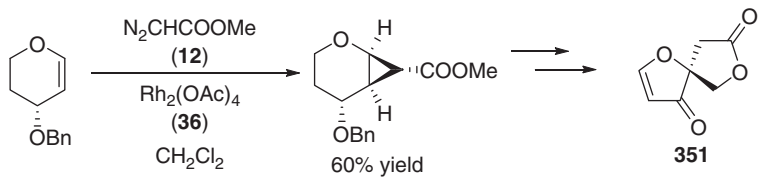
The key step in the total synthesis of the (+)-quebrachamine **296**, an alkaloid obtained from the dried bark of the tree *Aspidosperma quebracho-blanco*, by Andersson and coworkers consists of the asymmetric cyclopropanation of 5-ethyl-3,4-dihydro-2*H*-pyran **350** by ethyl diazoacetate **12** using Cu-**293** as a catalyst (Scheme 47).[833]



Scheme 47

4.20.4.1.6.10 (−)-Longianone

(*S*)-(−)-Longianone **351** is a metabolite produced by the fungus *Xylaria longiana*. The enantioselective synthesis of (−)-longianone by Perali and Karapati involves the $Rh_2(OAc)_4$ **36**-catalyzed reaction of (*R*)-4-benzyloxy)-3,4-dihydro-2*H*-pyran **352** with methyl diazoacetate **54** (Scheme 48).[864] The corresponding cyclopropane was obtained as one stereoisomer in 60% yield.



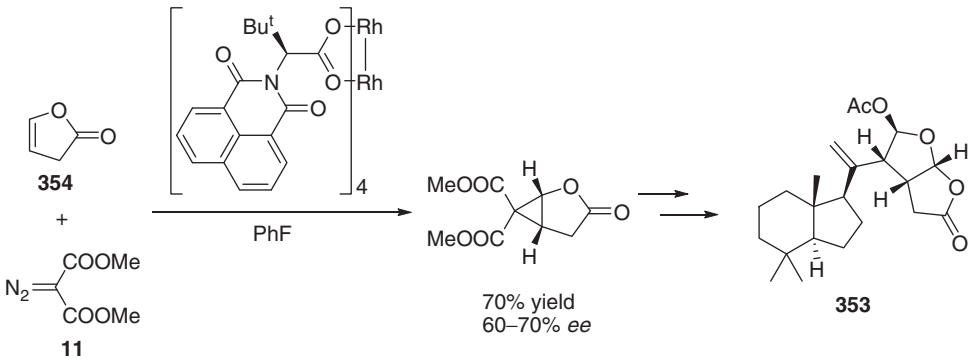
Scheme 48

4.20.4.1.6.11 Norrisolide

Norrisolide **353** is a marine natural product isolated from the nudibranch mollusc *Chromodoris norrisi* and some sponges of the same area. The first step of the synthesis of norrisolide by Granger and Snapper consists of the reaction between furan-2(3*H*)-one **354** and dimethyl diazomalonate **11** in the presence of Müller's catalyst.[865] The reaction carried out by slow addition of the diazo compound leads to a 70% yield with 60–70% *ee*. After cyclopropanation, Müller's catalyst can be precipitated with acetonitrile and reused with the same efficiency (Scheme 49).

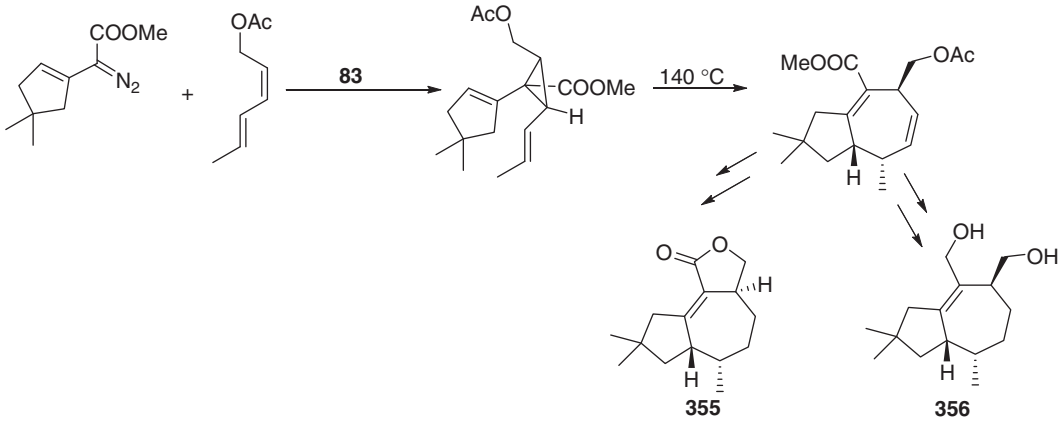
4.20.4.1.6.12 (±)-Tremulenolide A and (±)-Tremulenediol A

Tremulenolide A **355** and tremulenediol A **356** are two metabolites generated by the fungal pathogen *Phellinus tremulae*. The critical step in the total synthesis of (±)-tremulenolide A **355** and (±)-tremulenediol A **356** by Davies and Doan consists on an



Scheme 49

$Rh_2(Oct)_4$ **83**-catalyzed cyclopropanation/Cope rearrangement (Scheme 50). Thus, the reaction of a vinyldiazoacetic ester with a diene in refluxing hexane led to a mixture of a *cis*-divinyl cyclopropane and the desired cycloheptadiene.[525] Owing to the crowded boat conformation of the transition state for the Cope rearrangement, distillation at 140 °C was required to obtain 49% yield.



Scheme 50

4.20.4.1.6.13 Bisabolane-type natural products

Compounds exhibiting a chiral benzylic carbon atom can be obtained by using the stereoselective cyclopropanation reaction of styrene derivatives. Among these compounds, the bisabolane diterpene family can be remarked, including (*S*)-(+)-curcumene **357**, obtained from rhizomes of *Curcuma aromatica salisb*, as well as (*S*)-(+)-nuciferal **358** and (*S*)-(+)-nuciferol **359**, isolated from the wood *Torreya nucifera*. By using a synthetic intermediate, (+)-erogorgiaene **360**, a diterpene occurring in the octocoral *Pseudopterogorgia elisabethae* Bayer, which exhibits antimycobacterial properties, can also be obtained.

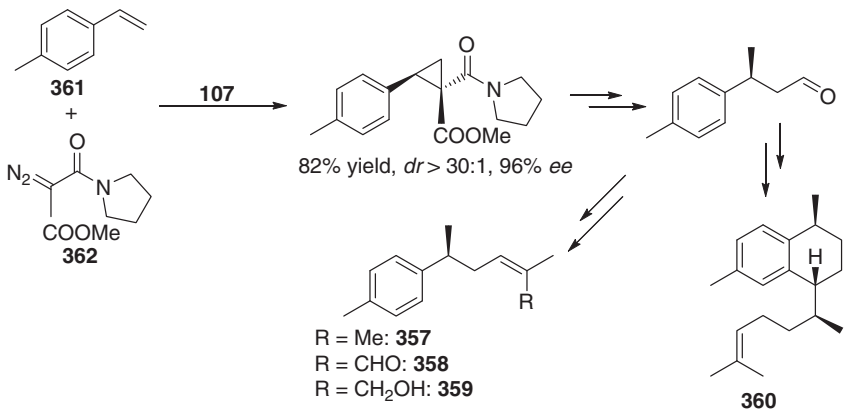
The reaction between *p*-methylstyrene **361** and methyl 2-diazo-3-oxo-3-(pyrrolidin-1-yl)propanaoate **362** catalyzed by Rh_2(*S*-NTTL)$_4$ **107** yielded the corresponding cyclopropane with excellent stereoselectivity (*dr* >30:1, 96% *ee*).[178] Such a compound can be transformed by keeping a high enantiomeric purity in (*S*)-3-*p*-tolylbutanal **363**, which can be used in the formal synthesis of (*S*)-(+)-curcumene **357**, (*S*)-(+)-nuciferal **358**, (*S*)-(+)-nuciferol **359**, and (+)-erogorgiaene **360** (Scheme 51).

Xanthorrhizol **364** and 2-hydroxycalamenene **365** are other members of the bisabolane family. Xanthorrhizol **364** is the major component of the essential oil of *Curcuma xanthorrhiza* and exhibits antibacterial activity against *Streptococcus mutans*. 2-Hydroxycalamene **365** has been isolated from plant origin with a significant fish-poison activity.

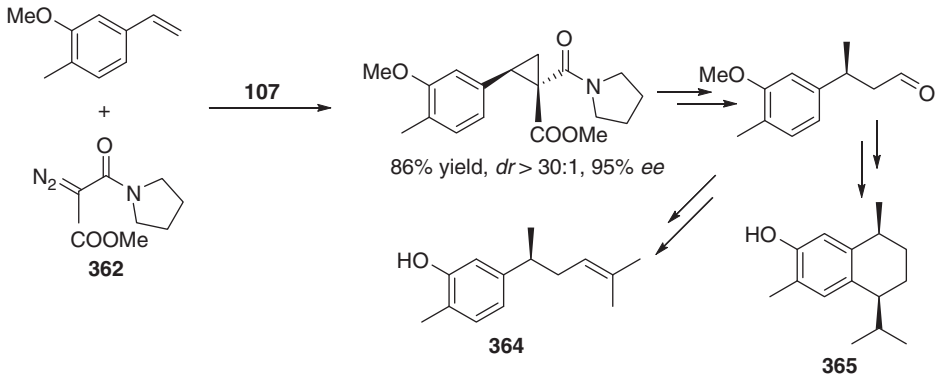
The reaction between 2-methoxy-1-methyl-4-vinylbenzene **366** and methyl 2-diazo-3-oxo-3-(pyrrolidin-1-yl)propanaoate **362** catalyzed by Rh_2(*S*-NTTL)$_4$ **107** yielded the corresponding cyclopropane in good yield (86%) and with excellent stereoselectivity (*dr* >30:1, 95% *ee*) (Scheme 52).[178] Such a compound can be transformed by keeping a high enantiomeric purity in (*S*)-3-(4-methyl-3-methoxyphenyl) butanal **367**, which can be used in the formal synthesis of **364** and **365**.

4.20.4.2 Intramolecular Reactions

The intramolecular reaction of a metal-carbenoid derived from an unsaturated carbonyl diazo compound was known since the early 1960s. This variant has demonstrated to be very useful for the synthesis of a large number of natural products, structural



Scheme 51

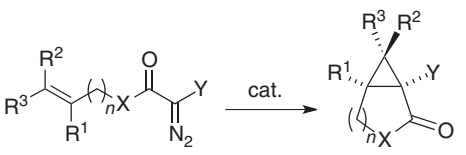


Scheme 52

analogs, and fully synthetic interesting compounds. This is partly due to the greater regio- and stereocontrol exhibited by the intramolecular version of these reactions. In this section some of these applications are updated and selectivity issues and the catalyst–substrate–selectivity relationships are also discussed. Several revisions and book chapters have been published covering the topic.[30,866–869]

First works dealing with intramolecular carbene addition reactions used copper compounds as catalysts, but little reaction selectivity was achieved with these catalysts. From the late 1990s, an increasing number of selective (chemo-, regio-, and stereoselective) catalysts have been described; most of them based on copper and rhodium metals, and also on ruthenium and cobalt, among others. In most cases, the catalysts share a common mechanism for the carbonyl diazo compound decomposition with subsequent formation of the metal–carbenoid intermediate (see Section 4.20.2.10). Other carbenoid precursors, as iodonium ylides, have also been used for intramolecular reactions, although to a lesser extent. Particular mention deserves enantioselective catalysts, as in many of the reactions reported catalysts are chiral and the products are obtained with good enantioselectivity in an almost routine manner. In the following sections, however, the reactions are organized by substrates, irrespective of the catalysts being enantioselective or not.

Although preference for five-membered ring formation is often observed, ring sizes up to 20 have been described, thus increasing the versatility of this synthetic strategy. The structure of the substrates generally used in these reactions can be summarized as shown in equation 88.



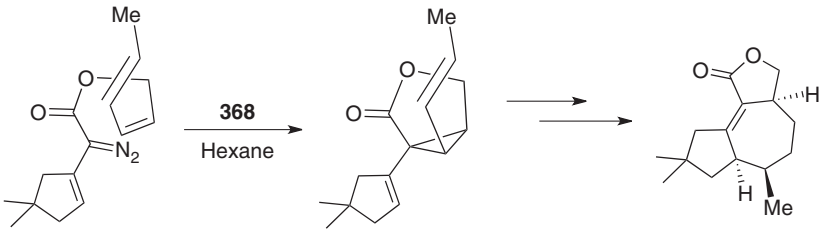
(88)

Y = H, Alkyl, aryl, COOR, COR, CN, PO_3R, SO_2R, SiR_3, NO_2,...
X = O, NR, CR_2, SiR_2
n = 0, 1, 2, ...
cat. = complexes of Rh(II), Cu(II), Ru(II), Co(II), Pd(II), Fe(II), ...

4.20.4.2.1 Alkenyl carbonylcarbenes leading to small size fused rings

Dirhodium(II) carboxylates have been tested in enantioselective intramolecular cyclopropanation (IMCP) reactions with little success.[109] Only a few successful cases have been reported, as the synthesis of seven-membered carbocycles, described by Davies and coworkers.[510] For other alkenyl diazoesters, only modest to moderate enantioselectivities are obtained with this kind of chiral catalyst.[870]

The 3+4 annulation strategy is a powerful convergent approach for the construction of seven-membered carbocycles. A highly stereoselective approach for the construction of seven-membered carbocycles by means of a tandem cyclopropanation/Cope rearrangement between rhodium-stabilized vinylcarbenoids and dienes has been described using the rhodium (*R*)-prolinate **368** catalyst (Scheme 53).[510,870]

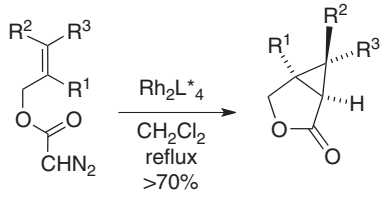


Scheme 53

Poor results have been also reported with a chiral rhodium porphyrin.[871] In contrast, dirhodium(II) carboxamidate catalysts, first described by Doyle et al.[539,872] have been used in the intramolecular cyclopropanation reaction (IMCR) of allylic diazoacetates, leading to the corresponding bicyclic lactones with moderate to good yields and enantioselectivities usually higher than 95% *ee*.[873–879] Enantioselectivities are noticeably poorer with diazo propanoates.[880] These reactions can be performed with 0.1 mol% of catalyst or less (usually $Rh_2(MEPY)_4$ **190** or $Rh_2(MPPIM)_4$ **369**) (Table 73).

$Rh_2(MEOX)_4$ **370** has also been used with substrates bearing a cycle in the allylic moiety, in the synthesis of bicyclo[3.2.2] nonadienones (Scheme 54).[881]

Table 73 Results obtained in the enantioselective intramolecular cyclopropanation of allylic diazoacetates, catalyzed by chiral rhodium carboxamidates

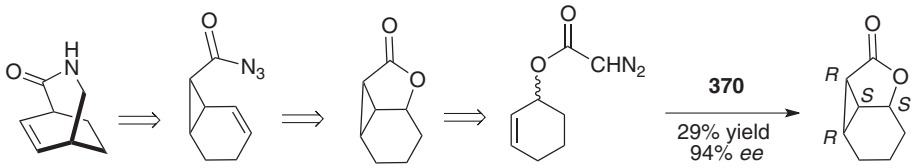


R^1	R^2	R^3	*Catalyst*	ee *(%)*
H	H	H	Rh_2(5*S*-MEPY)$_4$**190**	95
H	CH_3	CH_3	Rh_2(5*S*-MEPY)$_4$**190**	98
H	Ph	H	Rh_2(5*S*-MEPY)$_4$**190**	>94
H	H	Ph	Rh_2(4*S*-MPPIM)$_4$**369**	96
H	I	H	Rh_2(5*S*-MEPY)$_4$**190**	>94
CH_3	H	H	Rh_2(4*S*-MPPIM)$_4$	89
H	$(CH_3)_2C{=}C{-}(CH_2)_2$	CH_3	Rh_2(5*S*-MEPY)$_4$**190**	93
H	CH_3	$(CH_3)_2C{=}C{-}(CH_2)_2$	Rh_2(5*S*-MEPY)$_4$**190**	95

When the alkenyl chain is branched, the C–H insertion reaction on the tertiary carbon atom becomes competitive, and this product may even be the major one. Preference for cyclopropanation or C–H insertion depends on the distance of the double bond in the alkenyl chain, but also on the rhodium carboxylate and the solvent used. In general, $Rh_2(OAc)_4$ **36** tends to favor C–H carbene insertion.[500]

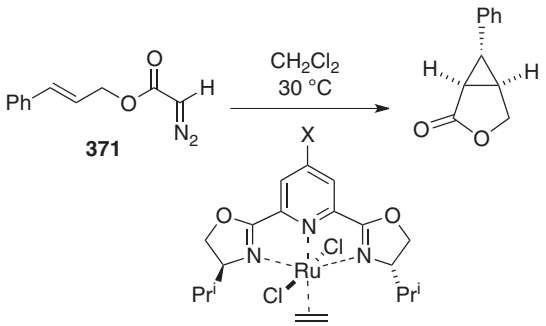
Rhodium catalysts usually outperform copper and ruthenium complexes in these reactions,[882] although moderate to good enantioselectivities have been described using a chiral β-diketonato Cu(II) complex as catalyst.[883]

Nishiyama and coworkers tested several ruthenium pybox complexes in the IMCP of (*E*)-cinnamyl diazoacetate **371**, with modest to moderate enantioselectivities (Table 74).[720]



Scheme 54

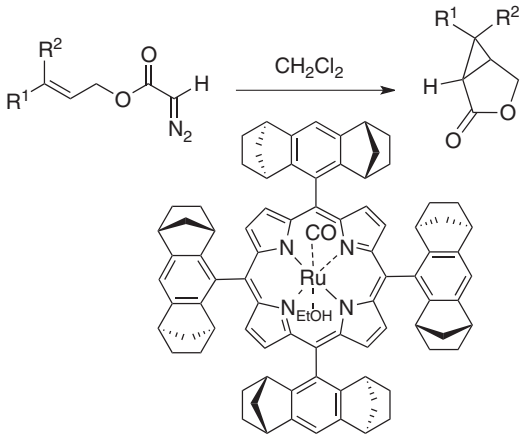
Table 74 Results obtained in the enantioselective intramolecular cyclopropanation of allylic diazoacetates, catalyzed by chiral rhodium carboxamidates



X	*Time (h)*	*Yield (%)*	ee *(%)*
$(CH_3)_2N$	41	67	52
CH_3O	12	73	78
H	2	83	86
Cl	2	80	85
CH_3OOC	0.33	72	89

Ruthenium porphyrin[92,93] and phtalocyanine[605] complexes have been tested in the intramolecular cyclopropanation of allylic diazoacetates, with rather moderate results (Table 75).

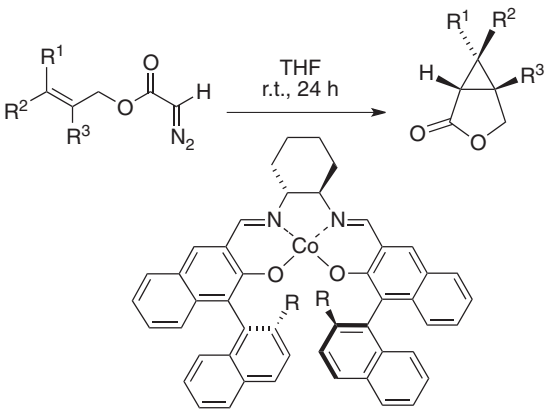
Table 75 Results obtained in the enantioselective intramolecular cyclopropanation of allylic diazoacetates, catalyzed by chiral ruthenium porphyrin



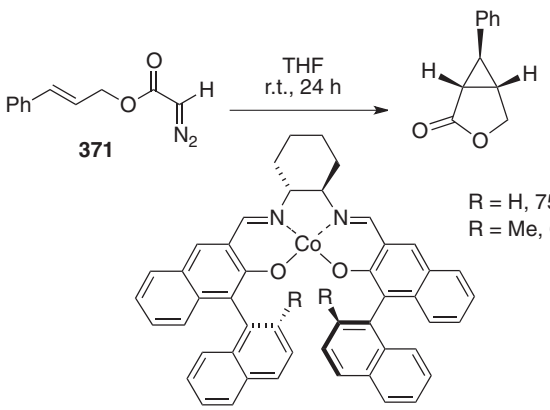
R^1	R^2	*Yield (%)*	ee *(%)*
H	H	45	24
CH_3	CH_3	65	36
H	CH_3	65	28
H	Ph	60	85
Ph	H	24	53

Somewhat better results were first reported by Katsuki and coworkers in the same reaction using different Ru(III)–salen and Co(II)–salen complexes.[641,884–886] By tuning the chiral ligand with the appropriate substituents, enantioselectivities more than 90% *ee* could be obtained with many substrates (Table 76).

Table 76 Results obtained in the enantioselective intramolecular cyclopropanation of allylic diazoacetates, catalyzed by chiral Co(II)–salen complexes

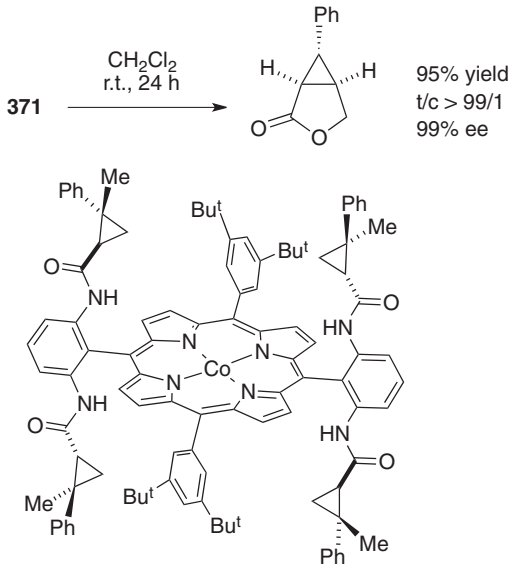


R	*R*^{1}	*R*^{2}	*R*^{3}	*Yield (%)*	ee *(%)*
CH_3	H	*p*-ClC_6H_4	H	72	98
H	H	*p*-ClC_6H_4	H	88	96
CH_3	H	*p*-$CH_3OC_6H_4$	H	70	98
H	H	*p*-$CH_3OC_6H_4$	H	93	96
CH_3	H	*p*-BrC_6H_4	H	70	97
H	H	*p*-BrC_6H_4	H	52	96
CH_3	H	PhC≡C	H	32	93
H	H	PhC≡C	H	24	84
H	H	$PhCH_2CH_2$	H	10	91
H	H	$PhCH_2CH_2$	H	48	82
H	H	$PhCH_2CH_2$	H	81	79
CH_3	H	$PhCH_2CH_2$	H	18	73
H	H	$(CH_3)_2CH$	H	34	75
CH_3	CH_3	Ph	H	70	90
H	CH_3	Ph	H	47	91
H	Ph	Ph	H	23	79
H	Ph	Ph	H	65	74
CH_3	Ph	Ph	H	35	81
CH_3	Ph	H	H	16	74
H	Ph	H	H	24	68
H	H	Ph	CH_3	12	38



(89)

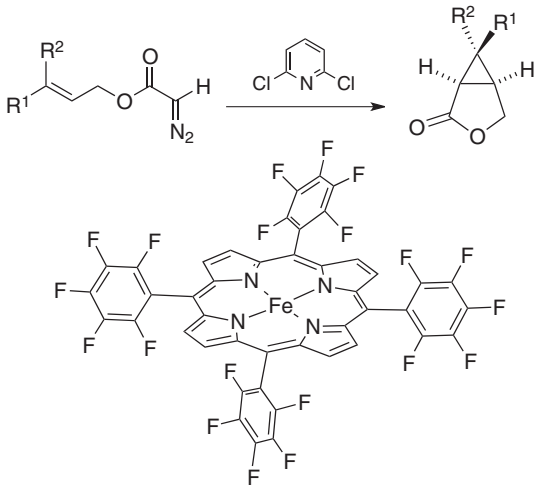
More recently, other Ru–salen catalysts have been described, also leading to good results.[887,888] Similarly, excellent results have been also described with a chiral cobalt–porphyrin complex, a new-generation catalyst for this kind of reaction.



(90)

It is also worth mentioning the good results obtained in the intramolecular cyclopropanation of allylic diazoacetates with a nonchiral iron–porphyrin complex (Table 77).[658]

Table 77 Results obtained in the intramolecular cyclopropanation of allylic diazoacetates, catalyzed by an iron porphyrin complex

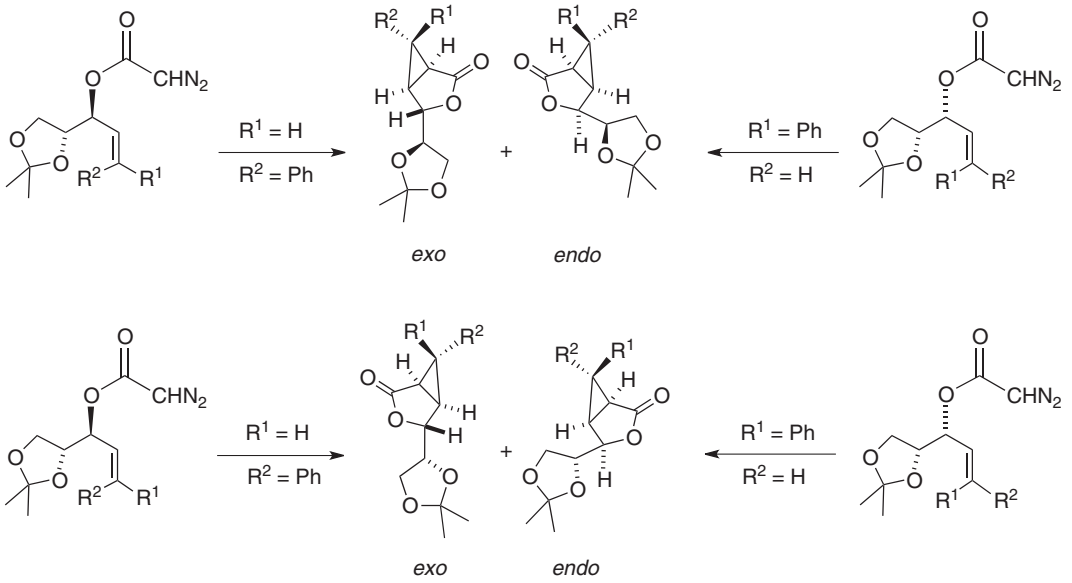


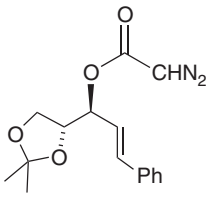
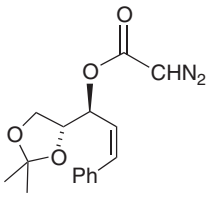
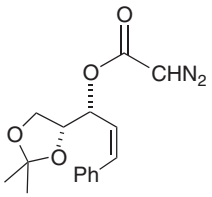
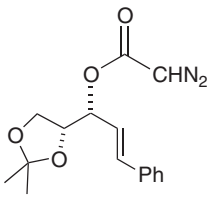
R^1	R^2	*Conversion (%)*	*Yield (%)*
Ph	H	100	76
CH_3	CH_3	100	92
Et	H	100	62
$(CH_3)_2C{=}C(CH_2)_2$	CH_3	84	73
CH_3	$(CH_3)_2C{=}C(CH_2)_2$	100	58

In some cases, the use of chiral auxiliaries has been used in combination with chiral catalyst to direct the stereoselectivity of the reaction toward one or another diastereoisomer (Table 78).[302]

The good performance of rhodium catalysts in the intramolecular cyclopropanation of diazoesters has allowed using this synthetic strategy in the preparation of natural products, such as Milnacipran, a clinically efficient antidepressant.[506] Good yields

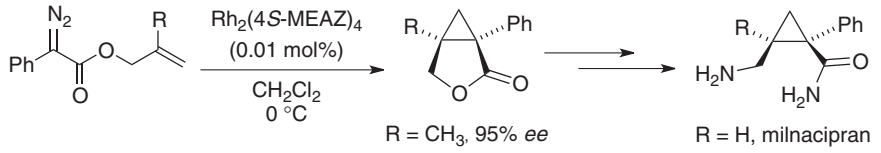
Table 78 Results obtained in the intramolecular cyclopropanation of chiral allylic diazoacetates, catalyzed by copper and rhodium complexes



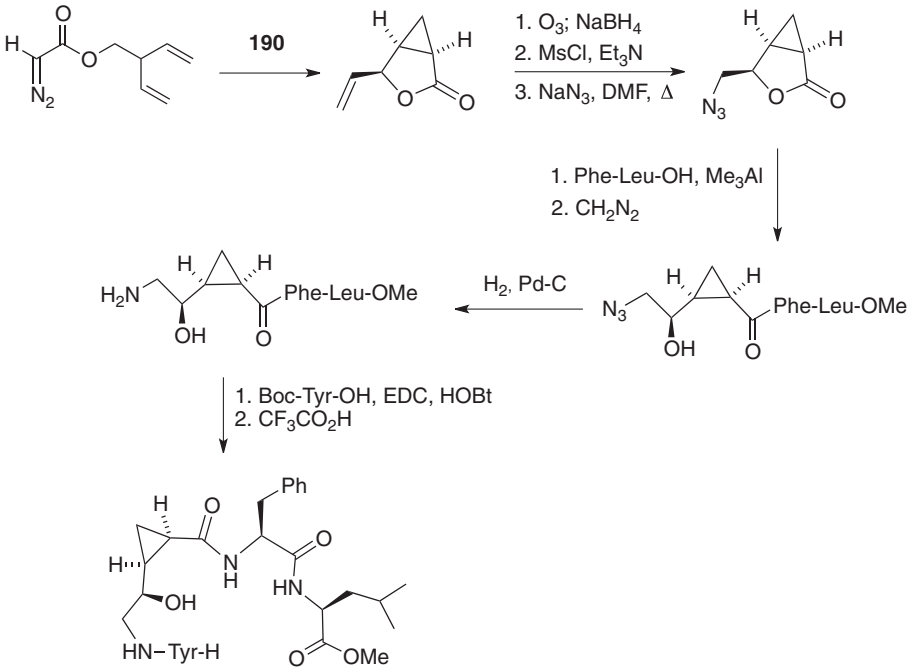
Substrate	*Catalyst*	exo	endo	*Combined yield (%)*
	$Cu(TBS)_2$ **132**	4	1	43
	$Rh_2(5S\text{-MEPY})_4$ **190**	2	1	64
	$Rh_2(5R\text{-MEPY})_4$ **372**	1	4	87
	$Cu(TBS)_2$ **132**	4	1	45
	$Rh_2(5S\text{-MEPY})_4$ **190**	1	–	2
	$Rh_2(5R\text{-MEPY})_4$ **372**	1	10	70
	$Cu(TBS)_2$ **132**	5	1	89
	$Rh_2(5S\text{-MEPY})_4$ **190**	1	3	83
	$Rh_2(5R\text{-MEPY})_4$ **372**	2	1	66
	$Cu(TBS)_2$ **132**	5	1	64
	$Rh_2(5S\text{-MEPY})_4$ **190**	1	20	56
	$Rh_2(5R\text{-MEPY})_4$ **372**	1.5	1	69

(more than 80% isolated yield) and moderate enantioselectivities (44–68% *ee*) are obtained with chiral dirhodium(II) azetidinone catalysts in the key cyclopropanation step (Scheme 55).

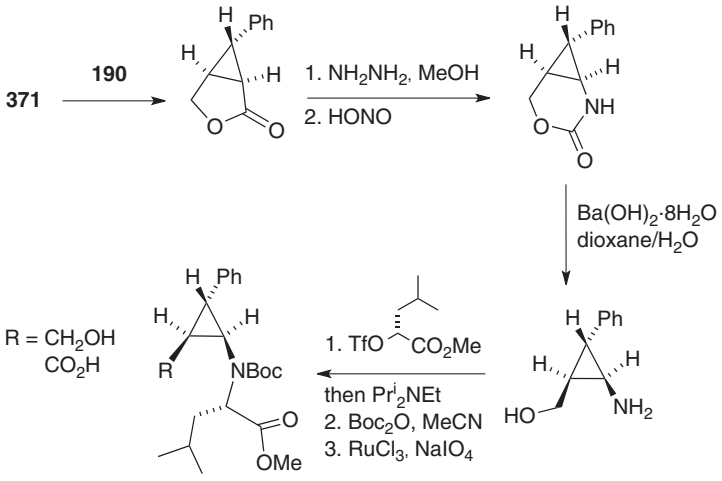
The intramolecular cyclopropanation of allylic diazoacetates has also been used in the synthesis of peptidomimetics. Thus, Martin and coworkers have described the synthesis of several classes of cyclopropane-derived peptidomimetics, like renin inhibitors,[889] HIV-1 protease inhibitors,[890] enkephalin analogs,[891] or Ras farnesyltransferase,[892] using the IMCR catalyzed by $Rh_2(MEPY)_4$, as the key step (Schemes 56 and 57).



Scheme 55

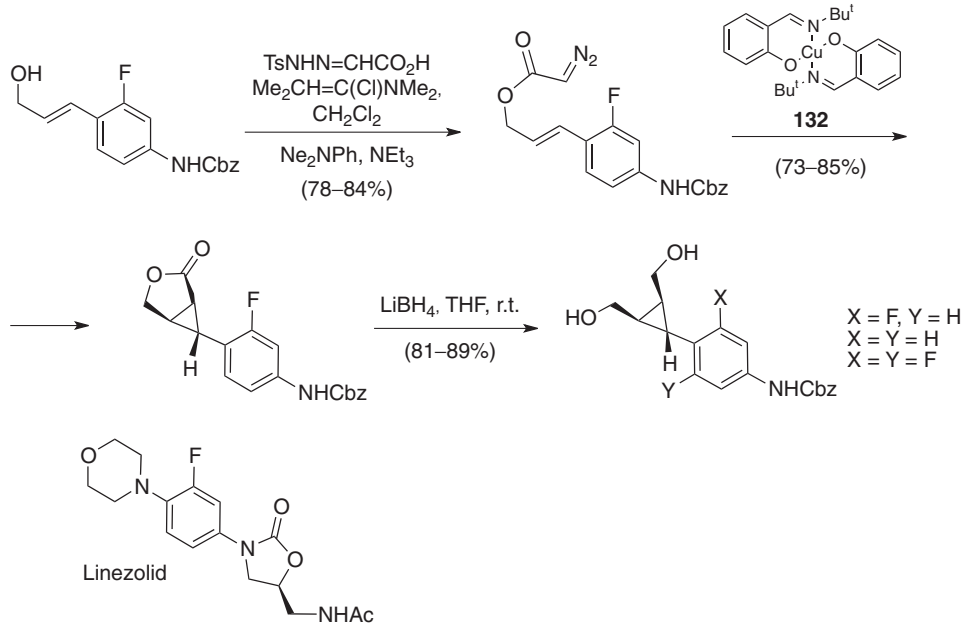


Scheme 56



Scheme 57

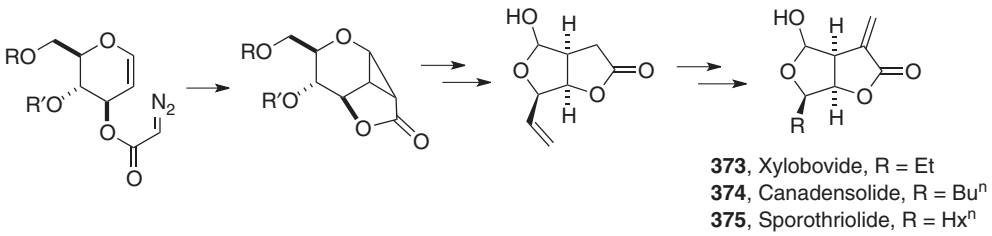
Aza-, oxa-, and thiabicyclo[3.1.0]hexane heterocycles may be viewed as conformationally constrained isosteres of well-known morpholine-, thiomorpholine-, or piperazine-substituted phenyloxazolidinones, such as linezolid (Zyvox), an antibacterial compound of the oxazolidinone class of bacterial protein synthesis inhibitors. The synthesis of these analogs has been carried out through IMCP reaction, catalyzed by $Cu(TBS)_2$ (**132**) (Scheme 58).[304]



Scheme 58

Carbon-branched sugars are interesting compounds, found in the glycon portion of many antibiotics and other natural products, and useful in the synthesis of indole alkaloids. IMCP reaction constitutes an interesting synthetic way to this kind of compounds. Thus diazoacetate esters of glucose-derived glycals can experience IMCP catalyzed by Cu(TBS)$_2$ **132** to give the desired intermediates.[303] Use of $Rh_2(OAc)_4$ **36** leads to lower yields in these systems. The cyclopropanic intermediates can then be transformed into xylobovide **373**, a natural phytotoxic, canadensolide **374**, a fungicide, or sporothriolide **375**, an antibacterial, fungicidal, algicidal, and herbicidal agent, demonstrating the versatility of the synthetic strategy (Schemes 59 and 60).

In contrast with their allylic counterparts, homoallylic diazoacetates show slightly poorer enantiocontrol with rhodium(II) carboxamidate catalysts, but still higher than that obtained with alternative catalytic systems (Table 79).[873]



Scheme 59

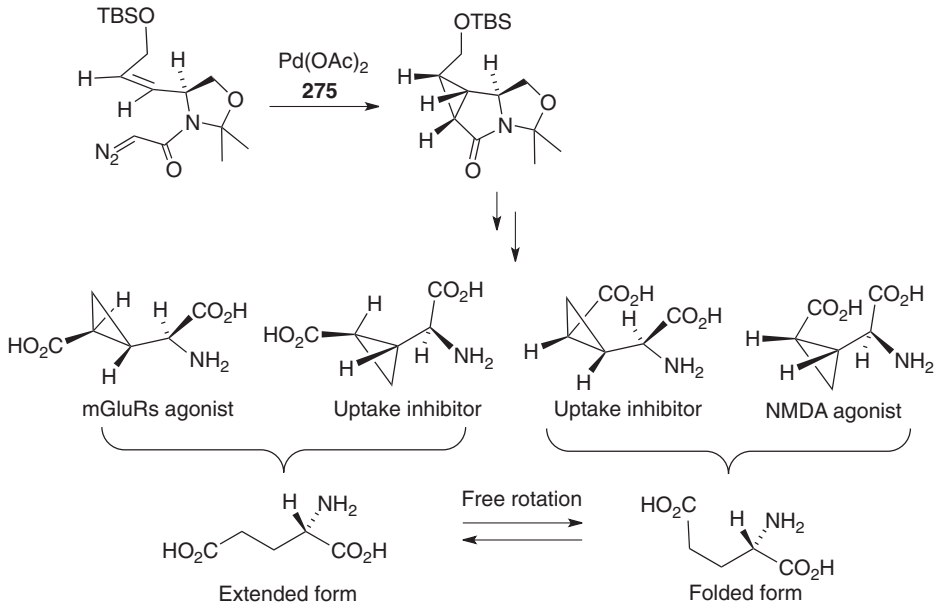
Closely related to the acetates, allylic and homoallylic diazoacetamides also give high enantiocontrol in reactions catalyzed by chiral dirhodium carboxamidates,[702,873,875] but only when there is not an N–H bond in the substrate (Table 80).

L-2-(2-carboxycyclopropyl)glycines (CCGs) and *L*-2-[2-carboxy-3-(methoxymethyl)cyclo-propyl]glycines (MCGs) are conformationally constrained analogs of L-glutamate **376**. The synthesis of these intermediates has been carried out by IMCP of allylic diazoacetamides, catalyzed by palladium acetate **275**,[671] with preference for the *exo* product. Reversed *endo*/*exo* selectivity is obtained in this step, when Rh and Cu catalysts are used instead.[300]

At least an example has been reported on the IMCP reaction using allenic compounds.[893] The catalyst used in this case was Cu(TBS)$_2$ **132** and the corresponding methylenecyclopropanes could be obtained with good diastereoselectivity in some cases (up to 90:10) (Table 81).

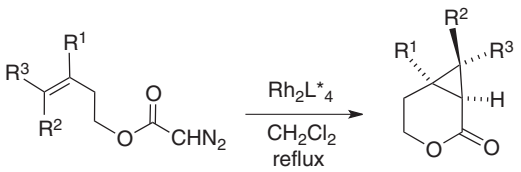
Other structurally similar substrates are allylic and homoallylic carbonyl diazo compounds bearing a second electron-withdrawing group. Thus, diazomalonic esters have also been used in intramolecular addition reactions, in combination with rhodium and copper catalysts.

Thus, the intramolecular carbene addition of different allyl *tert*-butyl diazomalonates, catalyzed by CuI **377**, leads to the corresponding lactones, which were subsequently transformed into 1-aminocyclopropane-1-carboxylic acids (Scheme 61).[894]



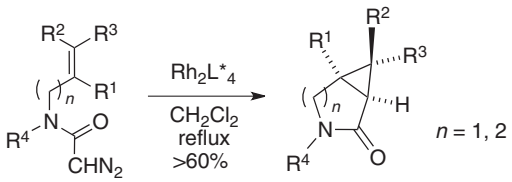
Scheme 60

Table 79 Results obtained in the enantioselective intramolecular cyclopropanation of homoallylic diazoacetates, catalyzed by chiral rhodium carboxamidates



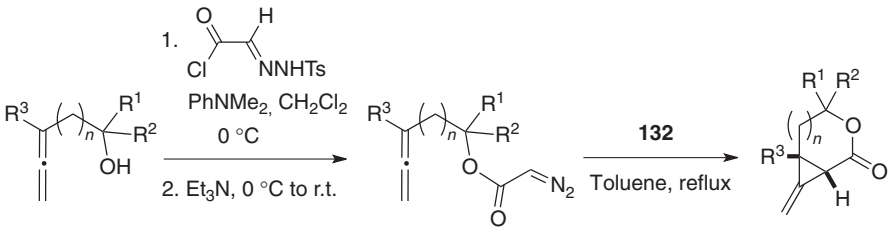
R^1	R^2	R^3	*Catalyst*	ee *(%)*
H	Et	H	Rh_2(5*S*-MEPY)$_4$	90
H	H	Et	Rh_2(5*S*-MEPY)$_4$	82
H	H	H	Rh_2(4*S*-MEOX)$_4$	83
CH_3	H	H	Rh_2(5*S*-MEPY)$_4$	83

Table 80 Results obtained in the enantioselective intramolecular cyclopropanation of allylic and homoallylic diazoacetoamides, catalyzed by chiral rhodium carboxamidates

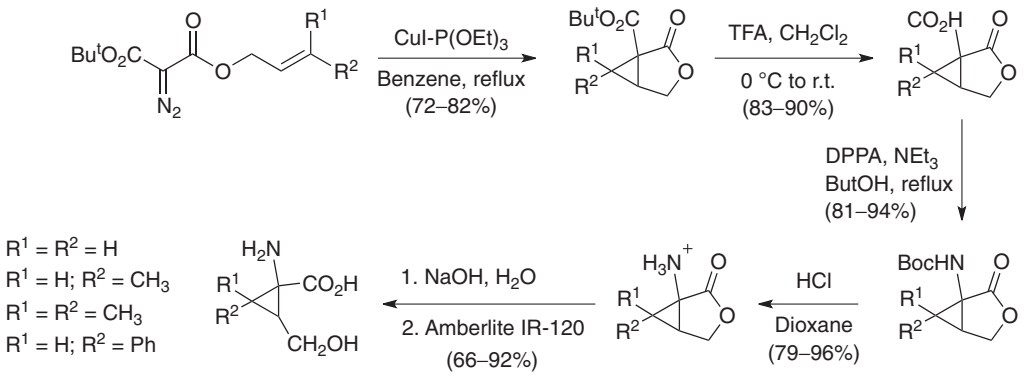


R^1	R^2	R^3	R^4	n	*Catalyst*	ee *(%)*
H	H	H	H	1	Rh_2(4*S*-MEOX)$_4$	98
H	CH_3	CH_3	CH_3	1	Rh_2(4*S*-MPPIM)$_4$	94
H	H	Pr^n	CH_3	1	Rh_2(4*S*-MPPIM)$_4$	92
H	Pr^n	H	CH_3	1	Rh_2(4*S*-MPPIM)$_4$	95
H	H	H	Bu^t	2	Rh_2(5*S*-MEPY)$_4$	60
H	CH_3	CH_3	Bu^t	2	Rh_2(5*S*-MEPY)$_4$	75
H	H	Et	Bu^t	2	Rh_2(5*S*-MEPY)$_4$	67
H	Et	H	Bu^t	2	Rh_2(5*S*-MEPY)$_4$	90

Table 81 Results obtained in the diastereoselective intramolecular cyclopropanation of allenes, catalyzed by $Cu(TBS)_2$ **132**



R^1	R^2	R^3	n	*Cyclopropane yield (%)*	dr
$-(CH_2)_5-$		H	0	94	–
CH_3	CH_3	H	1	76	–
H	H	H	2	–	–
H	Ph	H	0	84	50/50
H	Hx^c	H	0	82	55/45
H	Bu^t	H	1	83	53/47
H	Ph	H	0	54	75/25
H	Hx^c	CH_3	0	89	65/35
H	Hx^c	$(CH_3)_3Si$	0	90	80/20
H	Ph	$(CH_3)_3Si$	0	90	85/15
H	Bu^t	$(CH_3)_3Si$	0	787	94/6
H	Hx^c	Bu^tPh_2Si	0	60	90/10

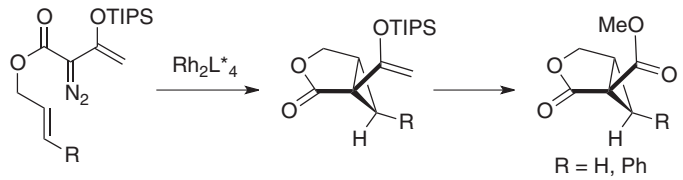


Scheme 61

Attempts to carry out the enantioselective version of this reaction using a bisoxazoline–copper complex, only led to modest enantioselectivities (10–15% *ee*).[895]

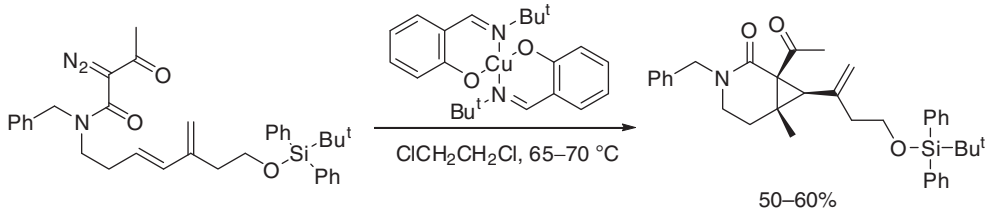
In fact, a further extensive testing of copper complexes with different chiral ligands led to disappointing results,[267] indicating the inappropriateness of these catalysts for the enantioselective transformation of these substrates.

Slightly better results have been described with a rhodium catalyst, but using *O*-silyl-protected diazoacetylacetic esters, namely (silanyloxyvinyl)diazoacetates. Up to 89% *ee* is described with moderate to good yields (Scheme 62).[896]



Scheme 62

An intramolecular reaction of an unsaturated α-diazo-β-ketoamide was tested with several catalysts in progress toward the total synthesis of (±)-actinophyllic acid.[189] A 50–60% yield was obtained with the $Cu(TBS)_2$ **132** catalyst (equation 91), other Cu and Rh catalysts leading to lower yields because of competing reactions.

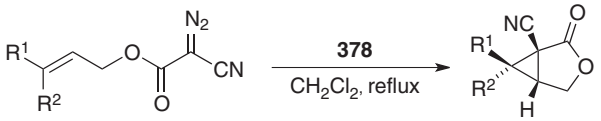


(91)

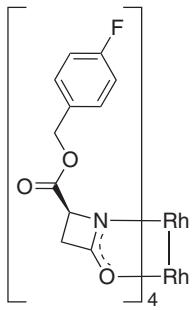
α-Cyano-α-diazoacetates are other related substrates that have been also tested in this kind of reaction. Rhodium catalysts are efficient with these substrates. Thus, the cyclization of different allylic α-cyano-α-diazoacetates proceeds smoothly and with good yields with $Rh_2(oct)_4$ **83**.[897]

After a screening of different chiral catalysts, $Rh_2(4S\text{-}(4')\text{-FBNAZ})_4$ **378** leads to the best results with different substrates, with enantioselectivities ranging from moderate to good in most cases (Table 82).[897]

Table 82 Results obtained in the enantioselective intramolecular cyclopropanation of allylic α-cyano-α-diazoacetates, catalyzed by $Rh_2(4S\text{-}(4')\text{-FBNAZ})_4$ **378**



R^1	R^2	*Yield (%)*	ee *(%)*
H	H	85	85
CH_3	CH_3	37	56
H	Et	53	n.d.
Ph	H	35	29
CO_2Et	H	32	80
Cl	H	11	n.d.
Br	H	27	87
I	H	21	75
H	Cl	43	77
H	Br	57	91
H	I	55	86
Br	Br	52	62
I	I	20	47

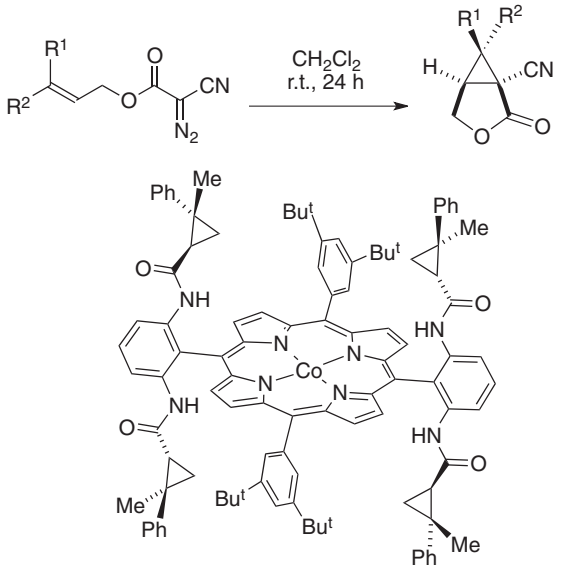


$Rh_2(4S\text{-}(4')\text{-FBNAZ})_4$

378

Even better results have been obtained with similar substrates, but using a chiral Co–porphyrin complex as catalyst (Table 83).[898]

Table 83 Results obtained in the enantioselective intramolecular cyclopropanation of allylic α-cyano-α-diazoacetates, catalyzed by a chiral Co–porphyrin complex

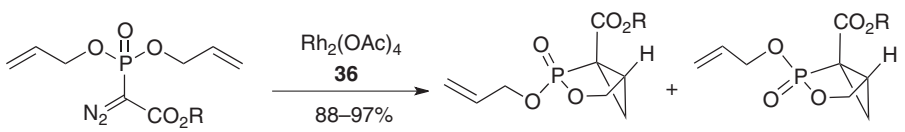


R^1	R^2	*Yield (%)*	trans/cis	ee *(%)*
H	Ph	99	>99:1	96
H	*p*-Bu^{t}C$_6$H$_4$	99	>99:1	96
H	*p*-CH$_3$C$_6$H$_4$	99	>99:1	98
H	*o*-CH$_3$C$_6$H$_4$	88	>99:1	97
H	*p*-BrC$_6$H$_4$	99	>99:1	95
H	*p*-CF$_3$C$_6$H$_4$	99	>99:1	95
H	2-furyl	51	>99:1	92
H	*N*-Boc-3-indolyl	93	>99:1	91
H	(*E*)-PhCH=CH	99	90:10	78
CH$_3$	(*E*)-PhCH=CH	88	>99:1	83
H	Et	99	>99:1	78
Et	H	99	36:64	69[a]/23[b]

[a] In *trans*-cyclopropanes.
[b] In *cis*-cyclopropanes.

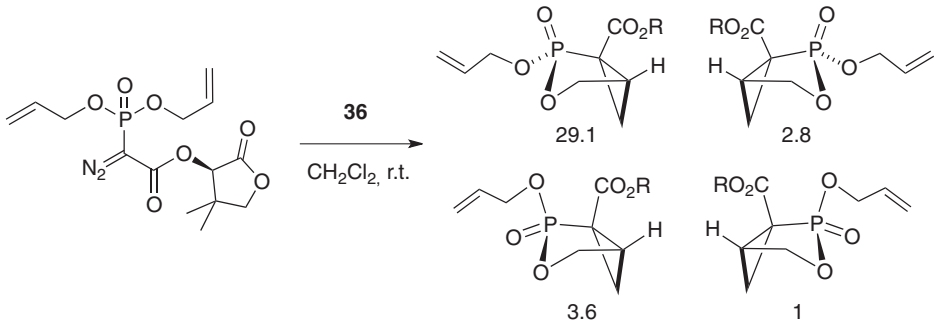
Other electronically similar substrates are α-diazo phosphonoacetates. $Rh_2(OAc)_4$ **36**-catalyzed intramolecular cyclopropanation of alkyl α-diazodiallylphosphonoacetates occur in good yield and with moderate levels of diastereoselectivity to yield *P*-heterocycles with a condensed cyclopropane ring (Table 84).[234]

Table 84 Results obtained in the intramolecular cyclopropanation of α-diazo phosphonoacetates, catalyzed by $Rh_2(OAc)_4$ **36**



R	*Yield (%)*	trans/cis
CH$_3$	97	2.5:1
Et	93	3.7:1
CH$_2$Ph	88	4.0:1
Bu^t	96	5.5:1

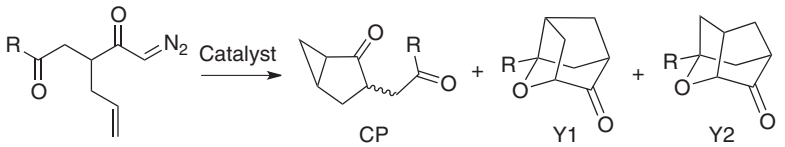
Similarly, bicyclic *P*-chiral phosphonates have also been prepared through a double diastereotopic differentiation strategy, based on an $Rh_2(OAc)_4$-catalyzed IMCP employing chiral auxiliaries in the ester functionality of the phosphonoacetate. The best results have been obtained with the (*R*)-pantolactone auxiliary **287**.[236,899]



(92)

Diazoketones are another big family of substrates used both in nonenantioselective and enantioselective IMCP reactions. Indeed, they are often the preferred intermediates for natural product synthesis (see Section 4.20.4.2.3). A comparative study on the use of several simple catalysts in the intramolecular cyclization of α-allyl-α-diazoketones revealed that copper and palladium catalysts were more selective than rhodium derivatives toward the addition product (**Table 85**).[679]

Table 85 Results obtained in the intramolecular cyclopropanation of α-diazoketones, catalyzed by different metal complexes



R	*Catalyst*	*Isolated yield (%)*	*Y1 yield (%)*	*Y2 yield (%)*	*CP yield (%)*	trans/cis
CH_3	$Rh_2(OAc)_4$ **36**	83	6	41	36	61:39
CH_3	$Rh_2(tfa)_4$	71	0	35	36	66:34
CH_3	$Cu(acac)_2$ **110**	94	0	9	85	91:9
CH_3	$PdCl_2(PhCN)_2$	89	0	0	89	93:7
Ph	$Rh_2(OAc)_4$ **36**	94	10	47	37	62:38
Ph	$Rh_2(tfa)_4$	93	34	12	47	36:64
Ph	$Cu(acac)_2$ **110**	98	9	35	54	63:37
Ph	$PdCl_2(PhCN)_2$	68	0	0	68	56:44

This synthetic strategy has been applied to the synthesis of prostaglandins and isoprostanes, a family of prostaglandin-like compounds.[491,900–902] Intramolecular cyclopropanation of the corresponding diazoketone, either catalyzed by $Rh_2(oct)_4$ **83** or $Cu(TBS)_2$ **132** complexes, leads to the intermediates that are further converted into the desired products (**Scheme 63**).

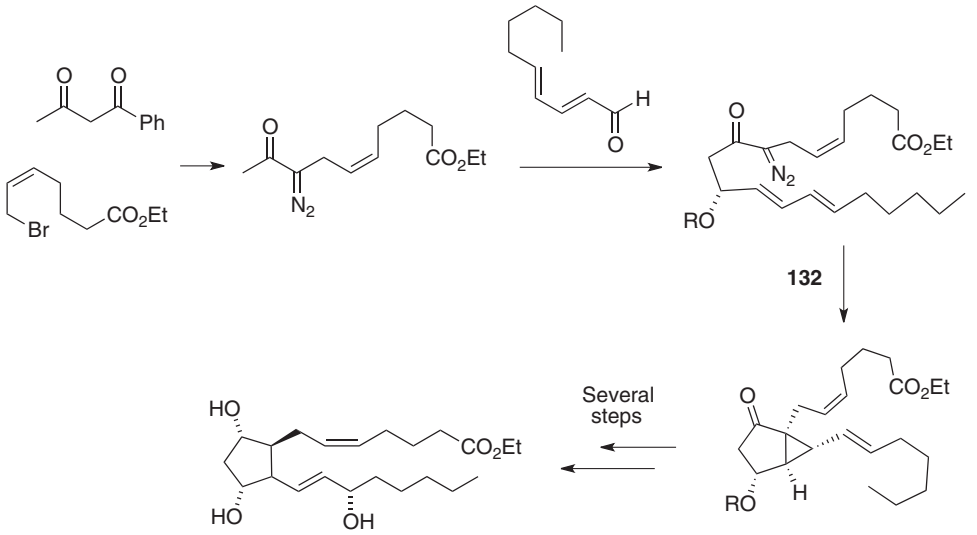
The preparation of constrained cycloalkyl analogs of glutamic acid with an ω-phosphonic acid function has been accomplished using diazoketones with the double bond functionalized with a phosphonate group (**Scheme 64**).[903]

Diazoketones lead to much worse enantioselectivity results than their diazoester counterparts, and in this case the use of copper–bisoxazoline complexes is often preferred over rhodium catalysts.[109,904–906]

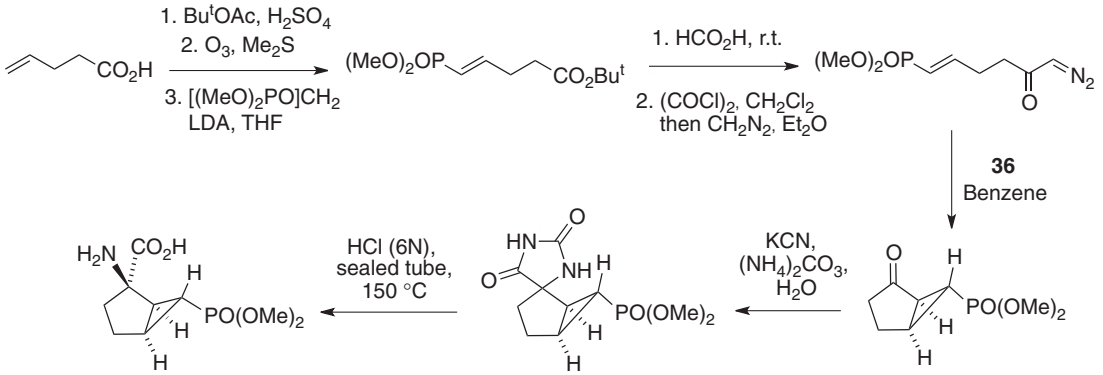
Excellent results have been described by Pfaltz and coworkers using chiral semicorrin–Cu(II) complexes.[383] However, the enantioselectivity obtained with these catalysts has a strong dependence on the structure of the diazoketone, so the methodology lacks generality.

However, high enantiocontrol can be achieved in the intramolecular cyclopropanation of diazo ketones using dirhodium(II) complexes with orthometalated aryl phosphine ligands as catalysts. Initial studies with nonchiral phosphines showed the good activities and selectivities toward IMCP of these catalysts.[907]

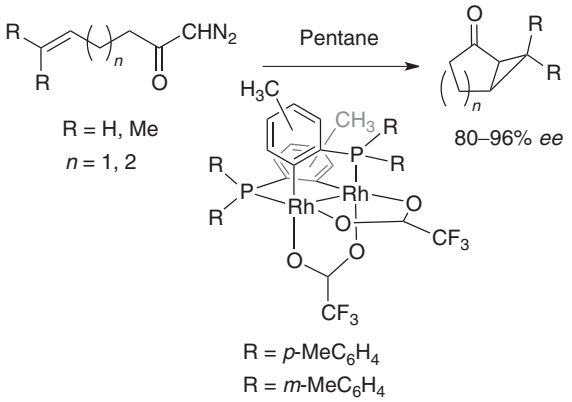
First studies with chiral catalysts were carried out on simple diazoketones, and excellent yields and enantioselectivities could be obtained with dirhodium(II) complexes with orthometalated aryl phosphine ligands: $Rh_2(O_2CF_3)_2(PCH)_2$ (PCH = triaryl phosphine).[908]



Scheme 63



Scheme 64



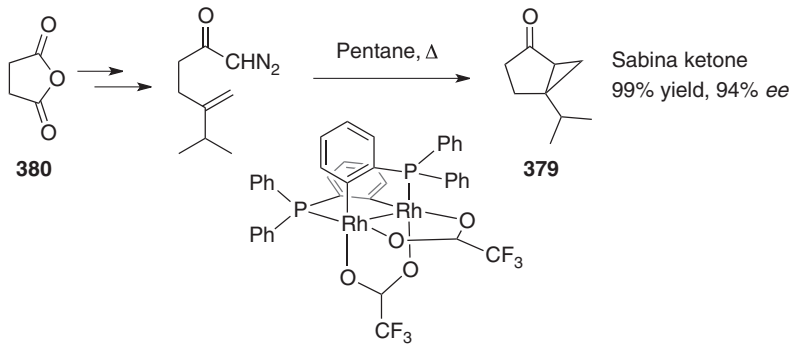
(93)

R = *p*-MeC$_6$H$_4$
R = *m*-MeC$_6$H$_4$

In a further work, the same researchers used the same catalysts in the synthesis of sabina ketone **379** from succinic anhydride **380**, with excellent yields and enantioselectivities.[909] Other researchers have also used variants of these catalysts with moderate to good results (Scheme 65).[541]

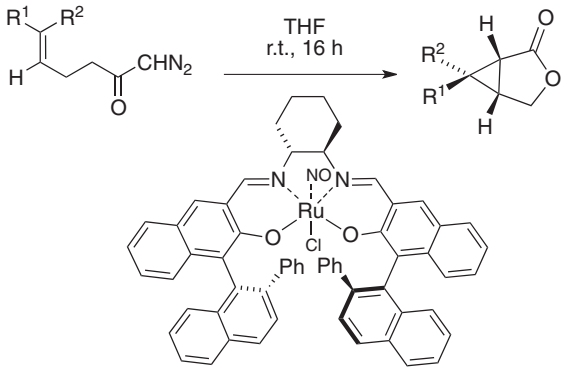
Regioselectivity and deracemization issues have also been addressed by these researchers.[910]

Good enantioselectivities with this kind of substrate have also been reported using chiral Ru(III)–salen complexes (Table 86).[641,886,911]



Scheme 65

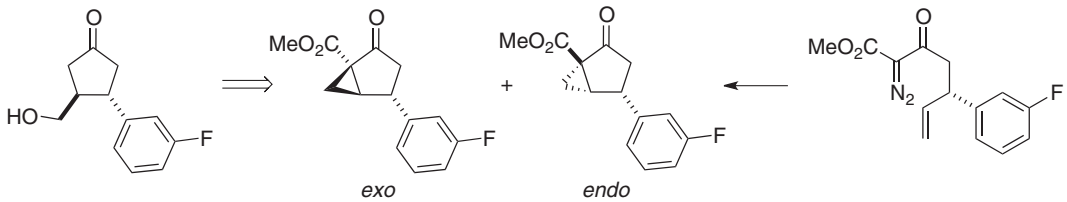
Table 86 Results obtained in the intramolecular cyclopropanation of α-diazo ketones, catalyzed by a chiral Ru(III)–salen complex



R^1	R^2	*Yield (%)*	ee *(%)*
$(CH_3)_2CH(CH_2)_2$	CH_3	72	93
CH_3	CH_3	65	87
PhC≡C	H	82	84
H	Ph	62	79
Ph	H	78	94

IMCP reaction of α-diazo-β-ketoesters, catalyzed by rhodium(II) hexanoate (**381**), has been used in the synthesis of highly strained tricyclic cyclopropanes.[912,913]

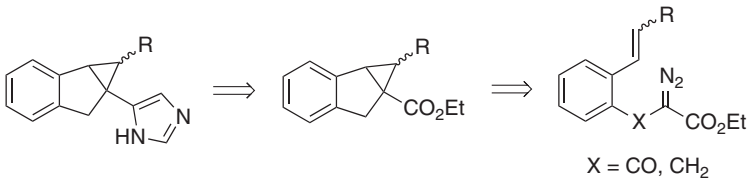
A practical route to chiral 3,4-disubstituted cyclopentanones has been developed using the IMCP of an α-diazo-β-ketoester as the key synthetic step for the final stereoselectivity. Rhodium and copper catalysts lead to opposite *endo*/*exo* ratio, the latter being more selective. Match–mismatch interactions with chiral catalysts were also investigated trying to improve the diastereoselectivity, but without success (Scheme 66).[914]



33	67	95% yield, $Rh_2(oct)_4$
83	17	98% yield, $[(CH_3CN)_4Cu]PF_6$

Scheme 66

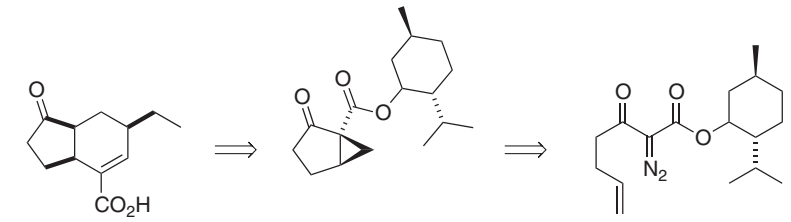
Similarly, these intermediates have been tested in the preparation of conformationally constrained α_2 antagonists of adrenergic receptors bearing a bicyclo[3.1.0]hexane structure,[915] although in this case the successful synthetic route used a β-diazo ester (Scheme 67).



Scheme 67

Diastereoselectivity induced by the presence of chiral auxiliaries in the ester group has also been investigated by several researchers, the best results being obtained with (*R*)-pantolactone **287** in the IMCP reaction catalyzed by $Rh_2(OAc)_4$ (up to 73:27) and bisoxazoline–copper complexes (up to 85:15),[458] whereas results were worse with (−)-menthol **284** and mixed carboxylate–phosphine rhodium(II) complexes (up to 65:35).[916]

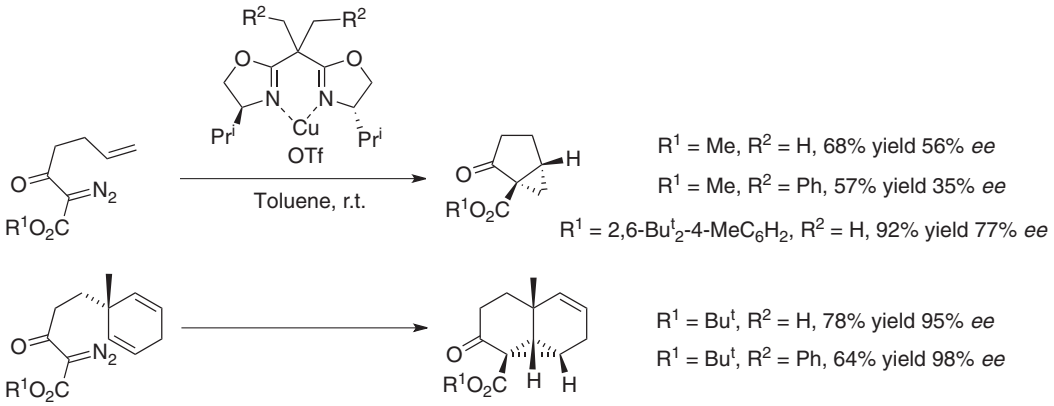
Similar diastereoselectivities (up to 75:25) have been obtained using rhodium pivalate **86** at low temperature, in the IMPC of the menthyl ester of an α-diazo-β-ketoester employed in the synthesis of (+)-coronafacic acid **382**, one of the components of the phytotoxin coronatin.[917] In this case, the use of chiral Rh catalyst does not improve diastereoselectivity (Scheme 68).



(+)-Coronafacic acid

Scheme 68

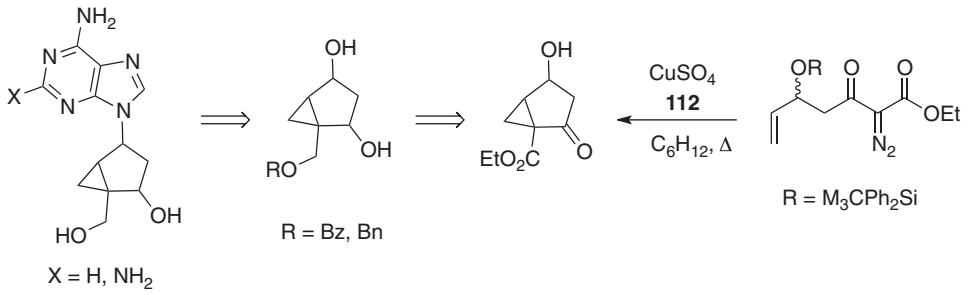
Similar to diazoketones, α-diazo-β-ketoesters lead to only moderate enantioselectivities in the IMCP reaction catalyzed by chiral copper complexes.[458,918] However, when some conformational rigidity is introduced in the substrate structure, enantioselectivity results dramatically improve by up to almost total selectivity (>95% *ee*).[919]



(94)

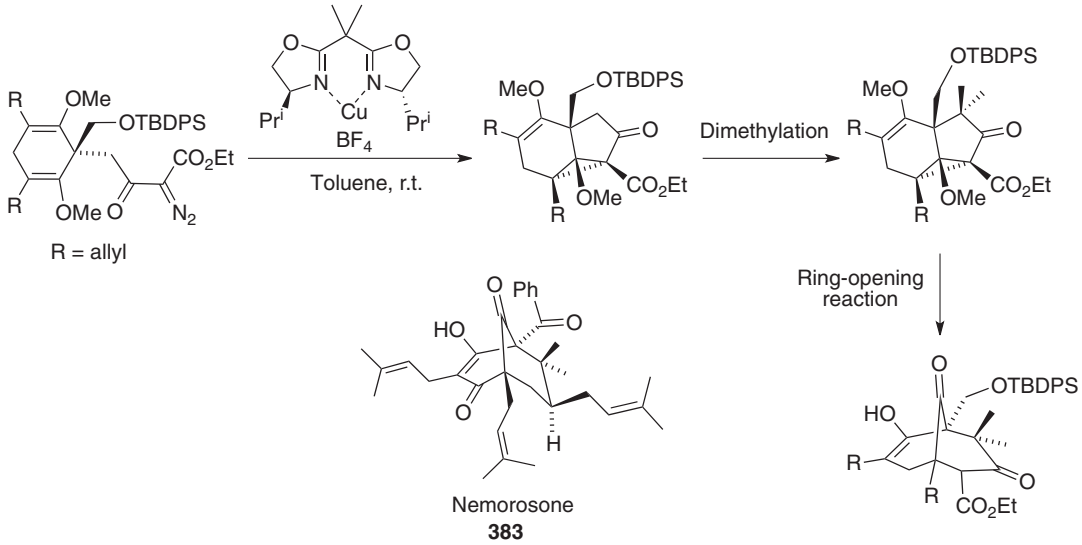
α-Diazo-β-ketoesters have been used as intermediates in the synthesis of carbocyclic nucleosides, which are interesting compounds because of their potential antiviral and antitumor activity. Thus, Marquez and coworkers described the intramolecular cyclopropanation of an α-diazo-β-ketoester precursor, catalyzed by $CuSO_4$ **112**, leading to a bicyclo[3.1.0]-hexane pseudosugar, which could be subsequently converted into the desired carbocyclic nucleosides (Scheme 69).[715,920]

Gallos et al. have also followed the same strategy to prepare analogous compounds.[448,921] Enantioselective α-diazo-β-keto ester IMCP has also been used in synthetic studies of nemorosone **383**, a member of the family of polycyclic polyprenylated



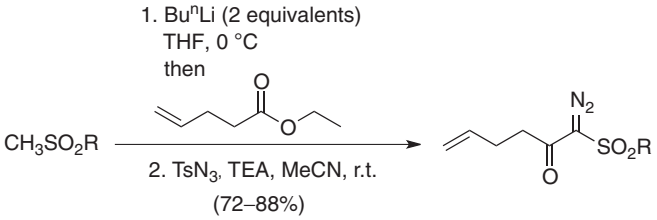
Scheme 69

acylphloroglucinols (PPAPs), which are known to have cytotoxicity against several human cancer cell lines.[922] In this case, chiral bisoxazoline–copper complexes were used as catalysts for the key step. However, the best results were obtained using an α-diazomethyl ketone as intermediate, with the **308**-$CuBF_4$ complex, but stoichiometric amounts of copper salt and 50% excess of ligand were required to have good yields and enantioselectivity (Scheme 70).



Scheme 70

α-Diazo-α-keto sulfones is another family of substrates that has proved to be of high interest in organic synthetic applications.[866] These substrates are quite stable and easily prepared by diazo transfer reactions of the corresponding β-keto sulfones, which are readily accessible by the reactions of the corresponding esters with the dianions of aryl methyl sulfones.[196]

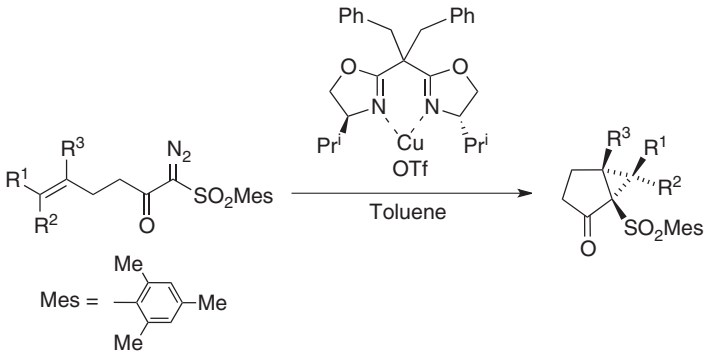


(95)

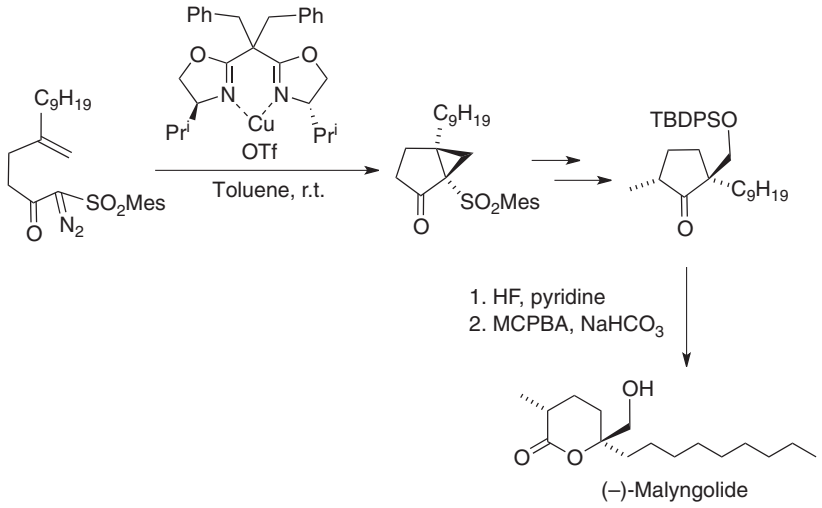
The intramolecular cyclopropanation reaction of different sulfones, catalyzed by chiral copper–bisoxazoline complexes, lead to good yields and enantioselectivities in optimum conditions, irrespective of the alkenyl chain of the sulfone substituent (Table 87).[196,866,923–925]

Owing to the good results obtained with these diazosulfone substrates, the intramolecular asymmetric cyclopropanation reaction has been used by Nakada and Honma as a key step in the total synthesis of a number of natural products,[866] such as (−)-malyngolide, (−)-methyl jasmonate, (+)-allocyathin B2, (−)-erinacine B, (−)-erinacine E, (+)-digitoxigenin,[926] (−)-scabronine A,[927] and (−)-platencin (Schemes 71–73).[928]

Table 87 Results obtained in the intramolecular cyclopropanation of α-diazo-α-keto sulfones, catalyzed by a chiral Cu(I)–bisoxazoline complex



R^1	R^2	R^3	*Yield (%)*	ee *(%)*
H	H	Me	90	98
H	H	Br	63	98
Me	Me	H	84	92
H	H	CH_2OTr	98	91
H	H	Ph	95	96

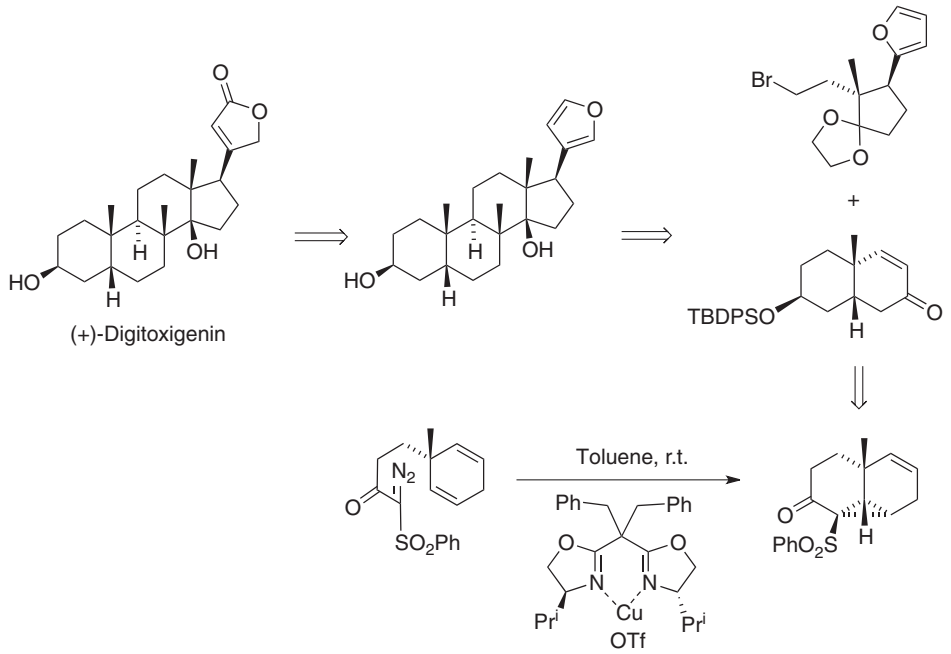


Scheme 71

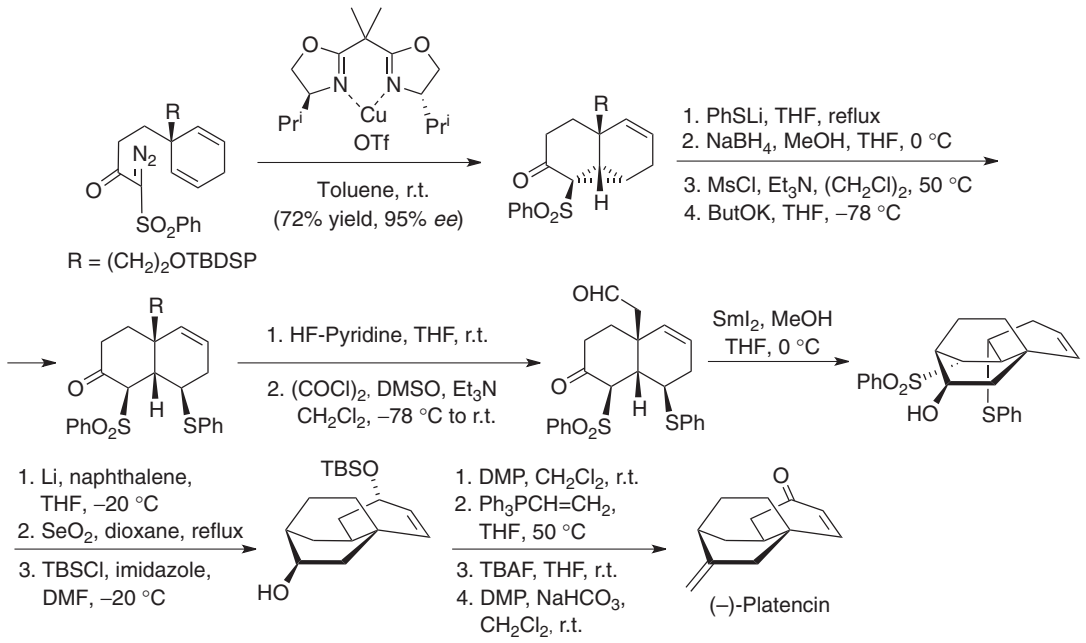
Carbonyl diazoesters bearing an electron-donor group, such as triethylsilyl, have also been used in IMCP reactions, catalyzed by rhodium complexes, although only modest enantioselectivities have been described.[224,226,227]

By inverting the relative positions of the silyl and ester groups, a new silyldiazoester is obtained, which is also able to react in the presence of a rhodium salt ($Rh_2(OOCC_3F_7)_4$ **384**) to give a rather unusual silabicyclo[2.1.0]pentane ring, which further evolves to the corresponding 2-[diisopropyl(methoxy)silylmethyl]cyclopropane-1-carboxylates **385** (Schemes 74 and 75).[230]

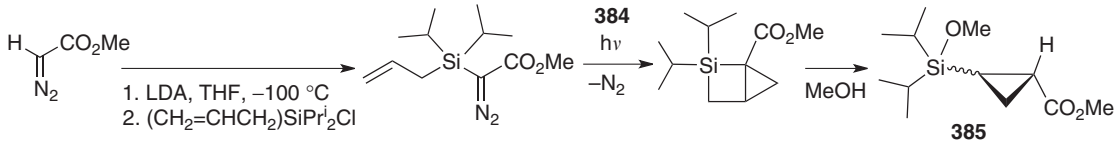
When (alkenoxy)silyl diazoacetates are used instead, the behavior is highly dependent on the substrate used.[231](Allyloxy)silyl diazoacetates lead to the corresponding silabicyclo[3.1.0]hexanes by the IMCP reaction catalyzed by Cu(I) triflate **78** or $Rh_2(pfb)_4$ **384**. In contrast, when the allylic double bond bears an electron-withdrawing group, only complex reaction mixtures are obtained with the same catalyst, and the thermal reaction only leads to the double-bond rearrangement product Finally, the [(3-butenyl) oxysilyl]diazoacetate **386** leads to the bicyclo[4.1.0]heptane system, no matter whether the reaction was carried out thermally, photochemically, or with transition-metal catalysis.



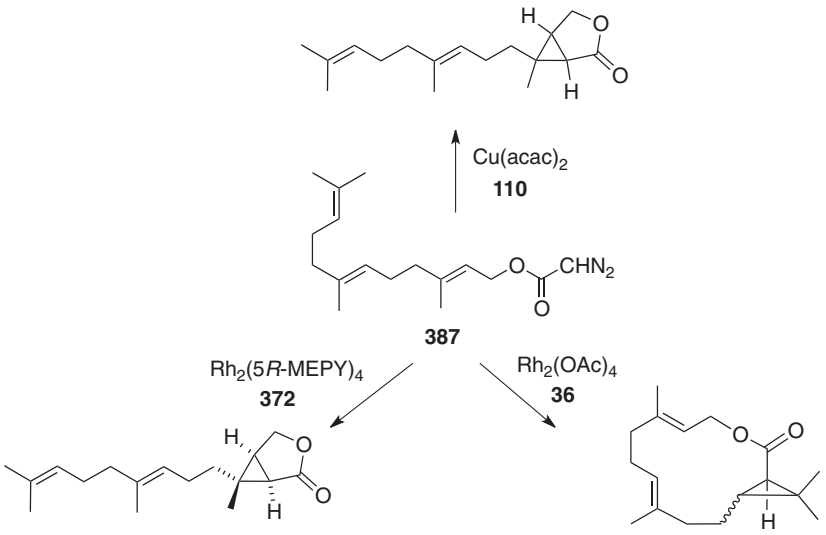
Scheme 72



Scheme 73



Scheme 74

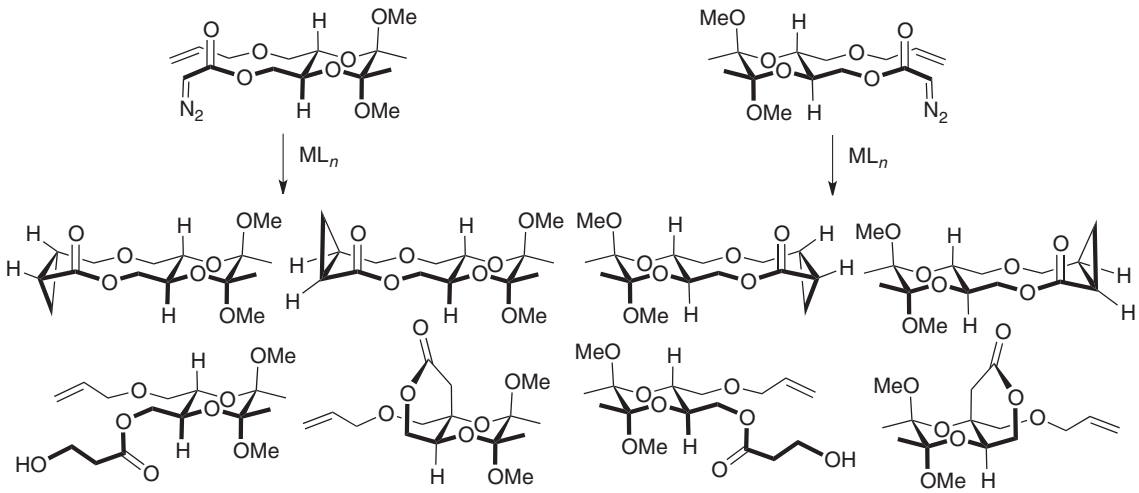


Scheme 75

4.20.4.2.2 Alkenyl carbonyl carbenes leading to medium-size and macrocyclic fused rings

By the mid-1990s, most intramolecular cyclopropanation reactions with carbonyl diazo compounds led to bicyclo[3.1.0] and bicyclo[4.1.0] rings. In some cases, as the intramolecular cyclopropanation reaction of *trans*,*trans*-farnesyl diazoacetate **387**, where there are several possible cyclization products, the preference for the small ring size was also observed.[929]

However, in 1995, Doyle et al. reported the formation of macrocyclic rings from the same precursor using dirhodium carboxylates as catalysts. The regioselectivity of the reaction depended to a large extent on the nature of the rhodium catalyst, macrocyclic products being favored with the simpler carboxylate complexes, as $Rh_2(OAc)_4$, **36** whereas rhodium carboxamidates led exclusively to the small ring product (Scheme 76).[930]

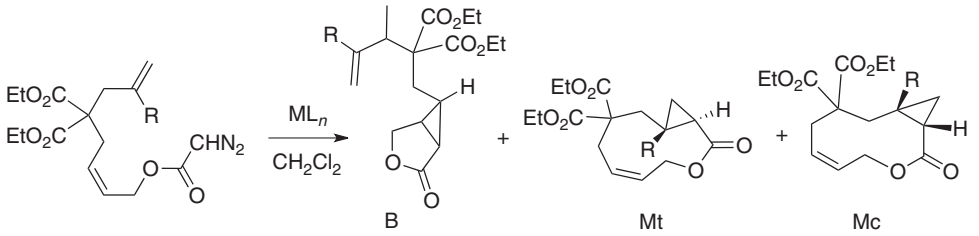


Scheme 76

These researchers also compared the behavior of chiral copper and rhodium complexes.[931] Thus, the use of a Cu–bisoxazoline complex led to the predominant macrocyclic compound, with moderate to good yields and good enantioselectivities, even in the case of a bicyclo[13.1.0] product. On the contrary, $Rh_2(MEPY)_4$ complex **190** led preferentially to the bicyclo[3.1.0] product. It is worth noting that in the macrocyclization reaction, the *cis* diastereoisomer of the cyclopropane is exclusively formed, contrary to that observed in intermolecular reactions, where *trans*-cyclopropanes are usually predominant.

A similar behavior has been observed with closely related subtrates, like malonic acid ester derivatives and pentaerithritol esters (Table 88).[288]

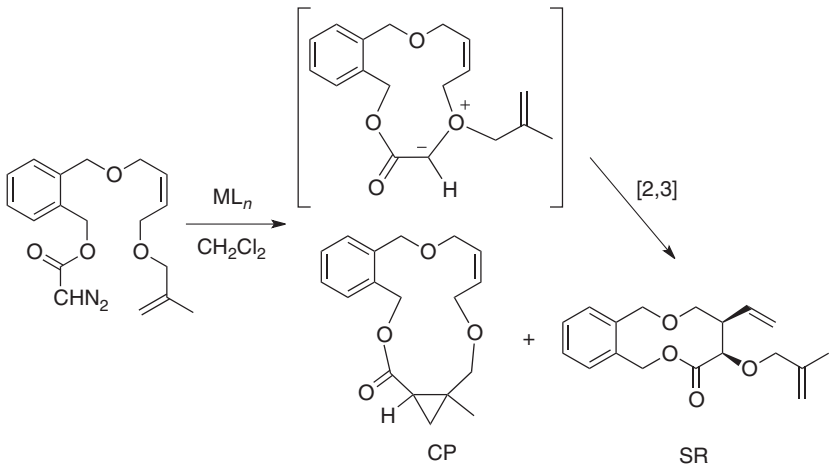
Table 88 Results obtained in the intramolecular cyclopropanation of malonic ester derivatives, catalyzed by different metal complexes



ML_n	R	Isolated yield (%)	Relative yield (%)		
			B	Mt	Mc
$Rh_2(pfb)_4$ **384**	H	68	1	44	55
$Rh_2(OAc)_4$ **36**	H	72	10	40	50
$Rh_2(cap)_4$	H	82	99	tr.	1
$CuPF_6$	H	66	5	35	60
$Cu(acac)_2$ **110**	H	55	100	–	–
$Rh_2(pfb)_4$ **384**	Me	87	4	–	96
$Rh_2(OAc)_4$ **36**	Me	87	4	–	96
$Rh_2(cap)_4$	Me	53	38	–	62
$CuPF_6$	Me	89	7	–	93

Another selectivity issue arises with the possible concurrence of tandem oxonium ylide formation-[2,3]-sigmatropic rearrangement reactions in the case of using 1,2-benzenedimethanol as linker in the macrocycle precursor. Product distribution is also very much dependent on the catalyst used (Table 89).[288,499,932]

Table 89 Intramolecular cyclopropanation vs. oxonium ylide formation product distribution as a function of the metal complex catalyst



ML_n	Isolated yield (%)	Relative yield (%)	
		CP	SR
$Rh_2(pfb)_4$	68	53	47
$Rh_2(OAc)_4$	71	94	6
$Rh_2(cap)_4$	65	>99	<1
$CuPF_6$	70	70	16

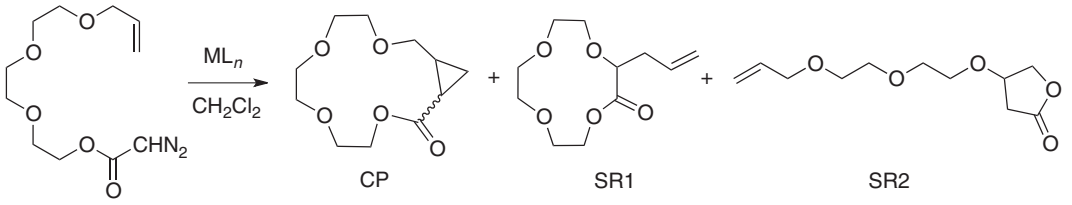
Abbreviation: SR, sigmatropic rearrangement.

The other double bond in the precursor is not so reactive. However, when the isobutenyl substituent is replaced by a methyl or a benzyl group, the corresponding cyclopropanation product appears, in concurrence with the rearrangement product. In general, the chemoselectivity of the catalysts favors the rearranged product in these cases.[499]

Of course, when the sigmatropic rearrangement is structurally disfavored, a total selectivity to the cyclopropane product is observed, irrespective of the catalyst used.[288]

A similar situation arises when ethylene glycol spacers are placed between the allyl group and the diazoacetate, and concurrence between cyclopropanation, C–H insertion, and oxonium ylide generation/[2,3]-sigmatropic rearrangement takes place.[519] Product distribution is highly dependent on the catalyst used. The simplest, nonchiral rhodium and copper catalysts favor the cyclopropane product. In this case, the best enantioselective catalyst is a copper–bisoxazoline complex (Table 90).

Table 90 Intramolecular cyclopropanation vs. sigmatropic rearrrangement product distribution as a function of the metal complex catalyst



ML$_n$	*Isolated yield (%)*	*Relative yield (%)*			ee *(%)*	
		CP	*SR1*	*SR2*	cis-*CP*	trans-*CP*
$Rh_2(OAc)_4$ **36**	65	97	0	3	–	–
$Cu(MeCN)_4PF_6$ **234**	65	86	14	0	–	–
293-$CuPF_6$	73	83	4	13	88	80
Rh_2(5*S*-MEPY)$_4$ **190**	61	13	0	87	49	44
Rh_2(4*R*-MEOX)$_4$ **388**	67	7	0	93	47	33

As already mentioned, C–H insertion can also be a concurrent reaction in some cases, and studies have been conducted to understand the influence of the reagent structure and the catalyst on this chemoselectivity (Table 91).[877]

Shorter substrates only lead to cyclopropane products, but from $n=3$, C–H insertion products also appear and their proportion is strongly dependent on the nature of the catalyst. The copper catalyst is always more selective toward the cyclopropanation products, C–H insertion products being negligible up to $n=8$. In contrast, rhodium catalysts display a more variable behavior, and depending on the ligand, C–H insertion products may become almost quantitative, as it is the case of the carboxamidates methyl 2-oxazolidone-4(*S*)-carboxylate (MEOX) and methyl phenylpropyl imidazolidinecarboxylato (MPPIM) with the substrate with $n=8$.

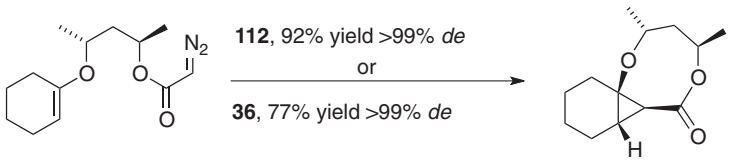
Another intriguing feature is that enantioselectivity displays an opposite behavior with copper and rhodium catalysts. The enantioselectivity of cyclopropane products increases with the length of the spacer in the first case, whereas it decreases in the second one (Figure 8).

A similar macrocyclization, using an α-nitrodiazoacetate and rhodium catalysts, has been described by Charette and coworkers.[205] Up to 61% *ee* with 66% yield is obtained in the best conditions.

Substrates with an oxygen heterocycle are also closely related. Tetrahydropyran derivatives have been used in the synthesis of ladder-like polycyclic ethers through C–H carbene insertion reactions. However, in some cases, the cyclopropanation product has been obtained as the sole product. The chemoselectivity is highly dependent on the catalyst used.[933]

1,4-Tetrahydropyran derivatives have also been studied by Doyle and coworkers. In this system, intramolecular C–H carbene insertion is also a concurrent process, as well as reaction of the diazo compound with water. The selectivity toward the cyclopropane products depends on the catalyst used and, in the case of the chiral rhodium catalysts, also on which enantiomer of the diazocompound is used (Scheme 76).[934]

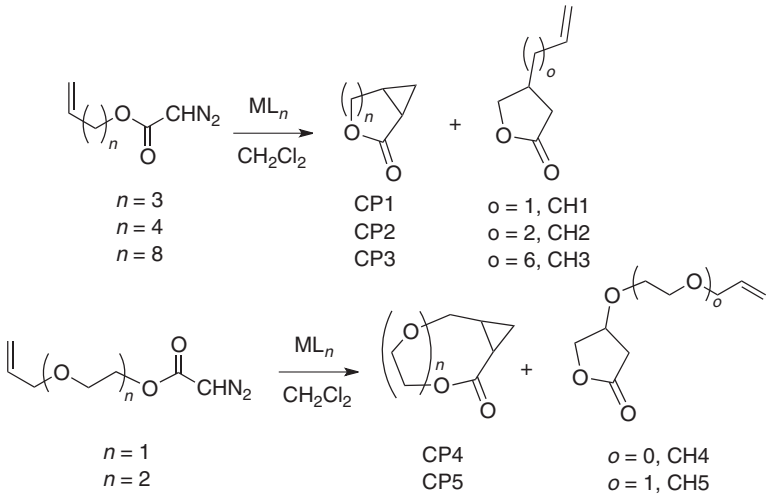
2,4-Pentanediol-tethered IMCP leads to medium-sized bicyclic structures. When enantiomerically pure 2,4-pentanediol is used, the IMCP reaction proceeds with total diastereoselectivity using a variety of metal catalysts, such as $CuSO_4$ **112** or $Rh_2(OAc)_4$ **36**.[935]



(96)

As a conclusion of this subsection, macrocyclization through intramolecular carbene addition reactions, mediated by metals, has become a very interesting synthetic strategy,[847,932,936] as these reactions do not require high dilution or other than the extraordinary conditions to achieve high product yields, and enantiocontrol parallels that found in intermolecular reactions.

Table 91 Intramolecular cyclopropanation vs. C–H insertion product distribution as a function of the metal complex catalyst



ML_n	*Chemoselectivity*					trans:cis	
	CP1:CH1	*CP2:CH2*	*CP3:CH3*	*CP4:CH4*	*CP5:CH5*	*CP3*	*CP5*
$Rh_2(OAc)_4$ **36**	>99:<1	84:16	68:32	82:18	96:4	31:69	13:87
$Rh_2(5S\text{-MEPY})_4$ **190**	42:58	14:86	4:96	<1:>99	5:95	25:75	12:88
$Rh_2(4R\text{-MEOX})_4$ **370**	19:81	9:91	1:99	<1:>99	1:99	24:76	12:88
$Rh_2(4S\text{-MPPIM})_4$ **369**	47:53	13:87	2:98	n.d.	n.d.	28:77	n.d.
$Rh_2(4S\text{-IBAZ})_4$ **420**	92:8	50:50	18:82	5:95	42:58	33:67	12:88
293-$CuPF_6$	>99:<1	>99:<1	86:14	–[a]	100:0	41:59	14:86

[a]The major product was that from intramolecular oxonium ylide formation followed by [2,3]-sigmatropic rearrangement.

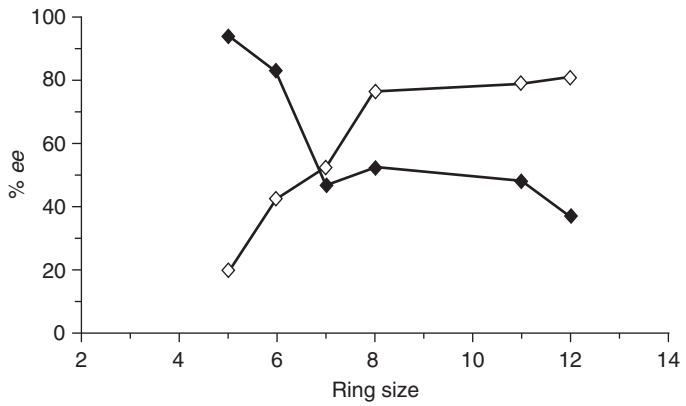


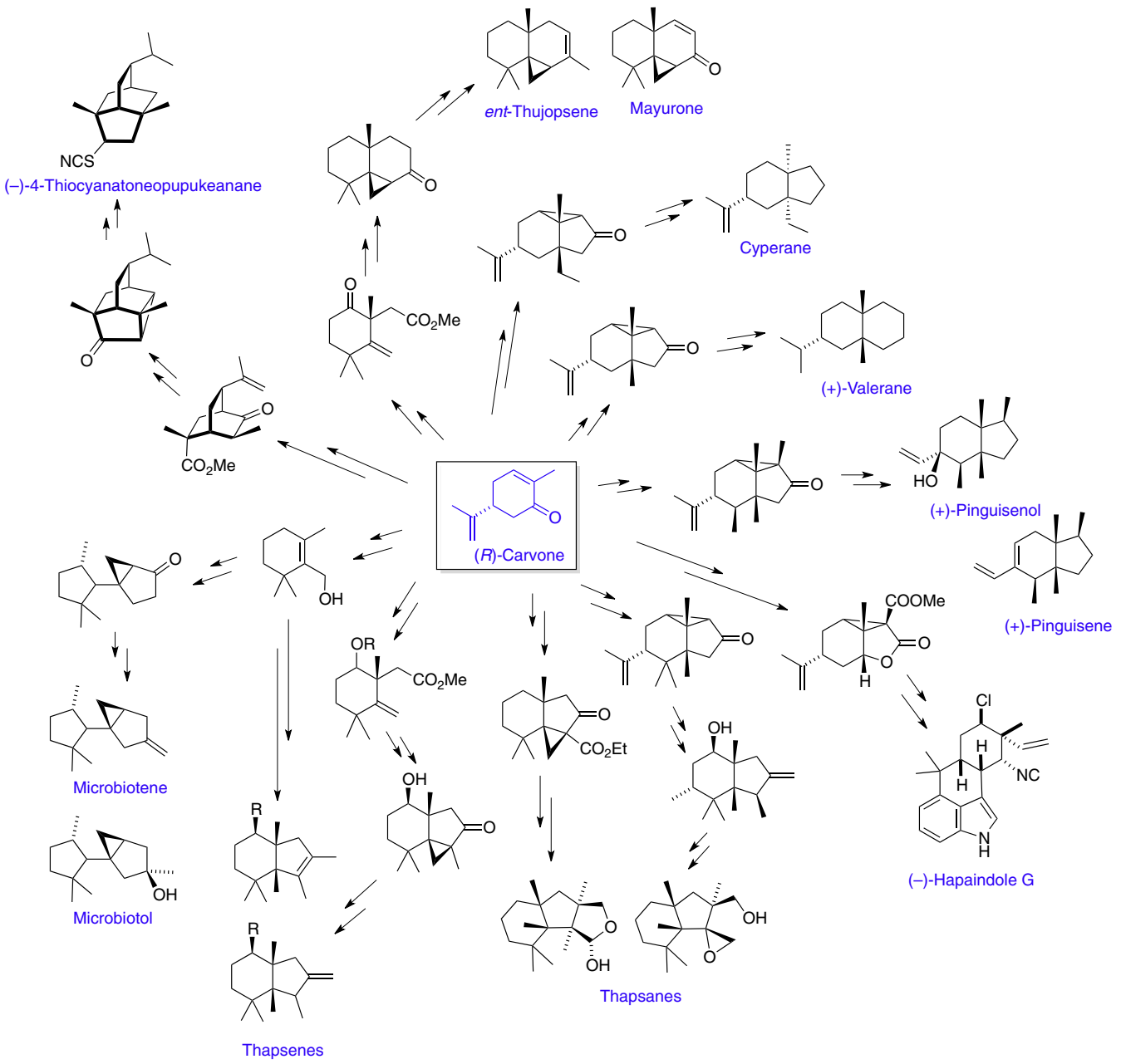
Figure 8 % *ee* as a function of ring size for Cu(box)PF_6 (◇) and $Rh_2(4S\text{-MEOX})_4$ (◆). Reprinted with permission from Doyle, M. P.; Phillips, I. M. *Tetrahedron Lett.* **2001**, *42*, 3155–3158.

4.20.4.2.3 Applications of intramolecular cyclopropanation reactions to total synthesis

The presence of two or more quaternary carbon atoms in a contiguous manner is a structural motif present in many natural products, and often represents a synthetic challenge. Intramolecular cyclopropanation reactions promoted by simple copper and rhodium salts have become an extremely useful synthetic tool in these cases. In this section, some examples of application of IMCP reactions in the synthesis of terpenes and other analogous natural products will be reconsidered.

4.20.4.2.3.1 Carvone as starting point for terpene synthesis

Srikrishna and coworkers have used IMCP reaction in the synthesis of natural products bearing two contiguous quaternary carbon atoms. In many cases, the starting point for the synthesis was simply (*R*)-carvone **389**. Scheme 77 shows some of the synthetic routes starting in this compound and leading to different terpenes through IMCP intermediates.


(–)-4-Thiocyanatoneopupukeanane
ent-Thujopsene
Mayurone
Cyperane
(+)-Valerane
(+)-Pinguisenol
(+)-Pinguisene
(R)-Carvone
Microbiotene
Microbiotol
Thapsenes
Thapsanes
(–)-Hapaindole G

Scheme 77

Stereo- and enantiospecific synthesis of (+)-valerane **390** starting from **389** has been achieved through an orthoester Claisen rearrangement and intramolecular diazoketone cyclopropanation reactions for the construction of the two vicinal quaternary carbon atoms.[277,281]

Intramolecular cyclopropanation is a key step in the total synthesis of (±)-*cis*,*anti*,*cis*-1,8,12,12-tetramethyl-4-oxatricyclo [6.4.0.0^{2-6}]dodecan-3-ol **391**, a thapsane isolated from *Thapsia villosa*. The intermediate diazoketoester reacts efficiently with an exocyclic double bond leading to a tricyclic structure. This reaction is promoted by $Rh_2(OAc)_2$ **36**.[283] Synthesis of (±)-3-methoxythapsene **392** has been achieved via stereospecific construction of three contiguous quaternary carbon atoms, employing a combination of a Claisen rearrangement and an intramolecular diazoketone cyclopropanation as the key reactions.[271] Enantiospecific synthesis of thapsanes, containing three contiguous quaternary carbon atoms, is accomplished starting from **389**.[272,276,459]

The total synthesis of (±)-*α*-pinguisene (±))-**393** and (±)-pinguisenol(±)-**394**, sesquiterpenes containing a *cis*-1,2,6,7-tetramethylbicyclo[4.3.0]nonane carbon framework incorporating two vicinal quaternary carbon atoms and four *cis*-oriented methyl groups on four contiguous carbon atoms, has been described employing an orthoester Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction for the stereospecific construction of vicinal quaternary carbon atoms.[279,280] The enantiospecific total synthesis of (+)-**394**, which was first isolated from a liverwort, has also been described.[278]

An enantiospecific approach to tricyclic sesquiterpenes mayurone **395** and thujopsenes, sesquiterpenes containing three contiguous quaternary carbon atoms, starting from **389**, has also been reported.[275]

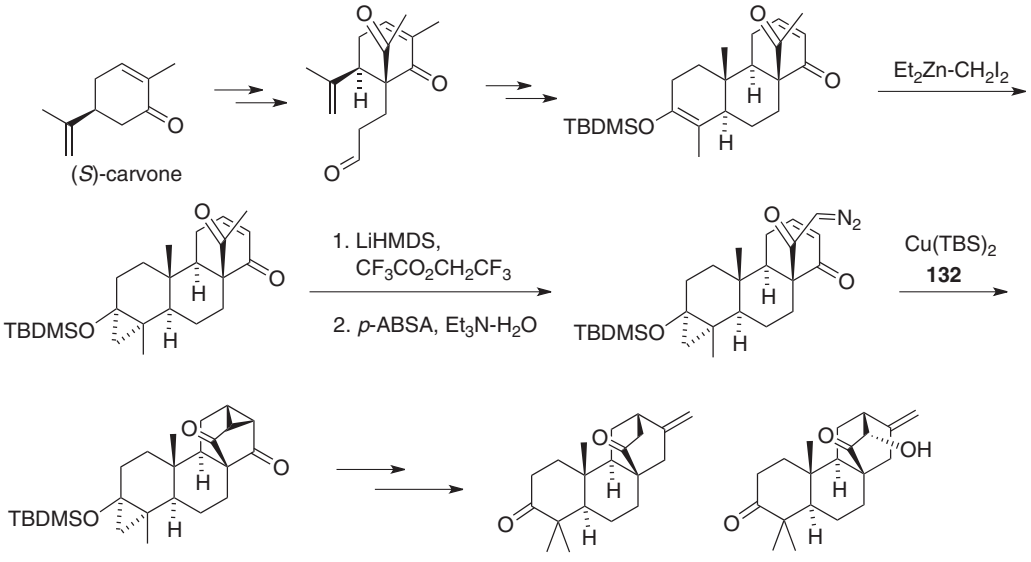
The first enantioselective total synthesis of (−)-microbiotol **396** and (+)-*β*-microbiotene **397**, sesquiterpenes containing three neighboring quaternary carbon atoms belonging to the cyclocuparane group, has been described starting from cyclogeraniol. This synthesis employs a Sharpless–Katsuki asymmetric epoxidation, a boron trifluoride etherate-mediated epoxide rearrangement and an intramolecular diazo ketone cyclopropanation, as the key steps.[270]

An enantiospecific approach to a functionalized carbon framework of the sesquiterpenes, cyperanes, starting from **389** has been accomplished. A combination of a Claisen rearrangement, intramolecular diazo ketone cyclopropanation and regiospecific cyclopropane ring cleavage has been exploited for the stereo and regiospecific generation of the vicinal stereogenic quaternary carbon atoms.[269]

A similar scheme, starting from **389**, has been used in the synthesis of (−)-hapalindole G **398**, a type of natural product isolated from the green algae. $Cu(TBS)_2$ **132** is used in the IMCP step.[298]

The enantioselective synthesis of the sesquiterpene (−)-4-thiocyanatoneopupukeanane **399**, which has been isolated from a marine sponge, has been accomplished through a tetracyclic cyclopropane obtained from intramolecular reaction of a chiral diazoketone, promoted by $CuSO_4$ **112**. As in other examples from this group, **389** is the ultimate source of chirality in the whole synthetic scheme.[937]

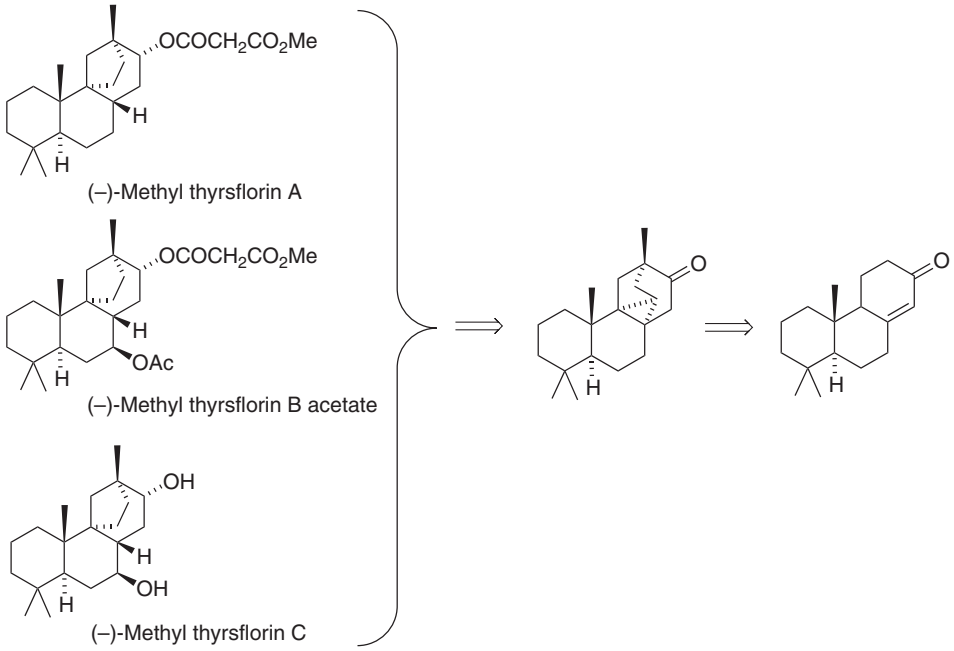
The construction of the complete carbon framework of atisene-type diterpenes from (*S*)-carvone (**400**) has also been described. This approach involves the initial preparation of a key atisane-type intermediate from **400**, using an intramolecular Diels–Alder reaction, an IMCR of an unsaturated diazoketone, catalyzed by **112**, and a regioselective endocyclic cleavage of the cyclopropane intermediate, as key synthetic steps (Scheme 78).[305,938]



Scheme 78

Structurally related to these compounds are the scopadulan diterpenes, first isolated from the alternative medicinal plant *Scoparia dulcis*. These compounds have shown interesting antiviral and antitumor activites.[939] A stereoselective synthesis of these

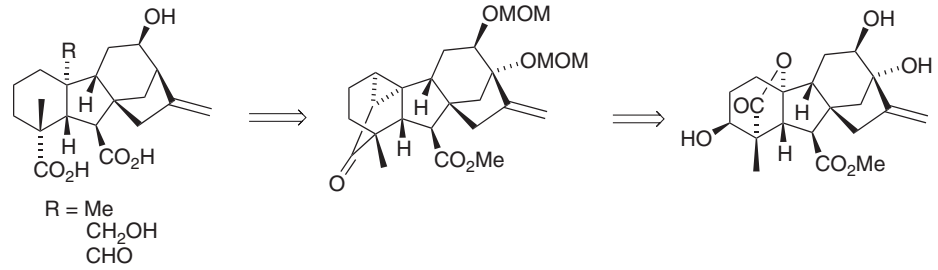
compounds has been described, which uses IMCP catalyzed by $Cu(TBS)_2$ **132** to form the skeleton of the tetracyclic final structures (Scheme 79).[940,941]



Scheme 79

4.20.4.2.3.2 2β-Hydroxy C-20 gibberellins

2β-Hydroxy C-20 gibberellins are natural products isolated from a number of plant sources, including tomato and barley. The confirmation of the tentative structural assignment has been accomplished through chemical synthesis.[301,942] IMCP reaction catalyzed by **132** is used as one of the steps of the synthetic scheme (Scheme 80).



Scheme 80

4.20.4.2.3.3 Oreodaphnenol

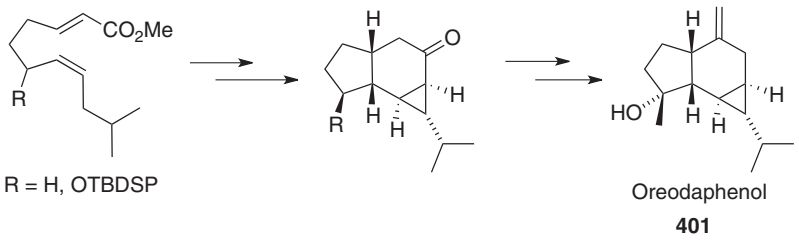
Oreodaphnenol **401**, a sesquiterpene alcohol isolated from Brazikan tree, *Oreodaphnena porous*, contains a 5-6-3 tricarbocyclic ring system. A synthetic scheme for this compound has been proposed, and partially carried out. The IMCP reaction of a diazoketone intermediate catalyzed by rhodium acetate is the key step to from the tricyclic system (Scheme 81).[446]

4.20.4.2.3.4 (±)-Albene

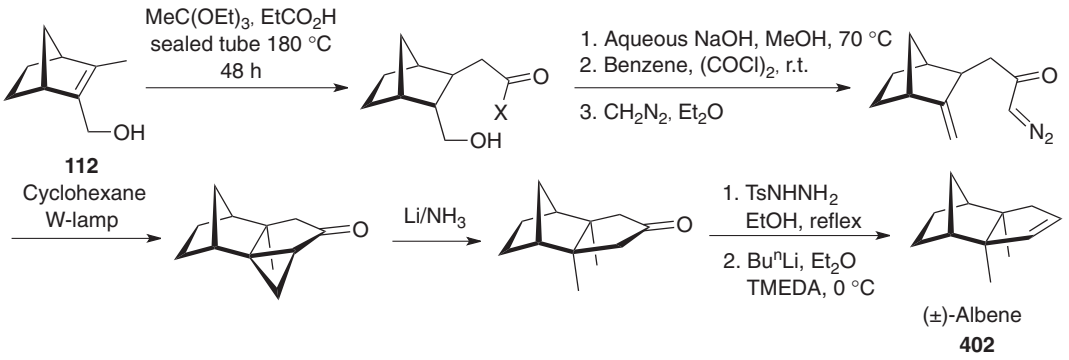
Trisnorsesquiternene (±)-albene **402** has also been synthesized from a Diels–Alder adduct, using the IMCP reaction to control the stereochemistry of the final product (Scheme 82).[282,943]

4.20.4.2.3.5 β-Chamigrene

The formation of two contiguous quaternary carbon centers in a spirocyclic compound is another example of challenging synthesis. Another example is the synthesis of β-chamigrene **403**, for which a methodology employing a $Rh_2(OAc)_4$-catalyzed

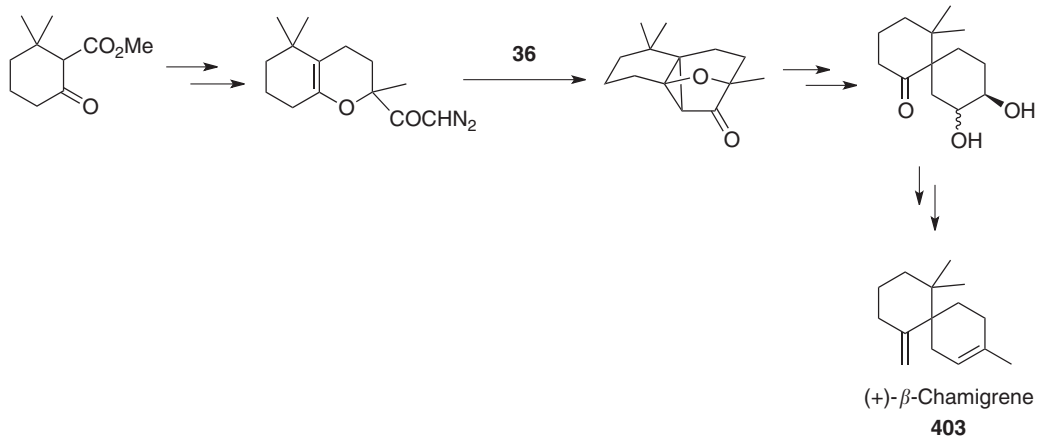


Scheme 81



Scheme 82

IMCP to a dihydropyran derivative, followed by sequential bond fragmentations produced the spirocyclic system precursor of the desired product (Scheme 83).[465]

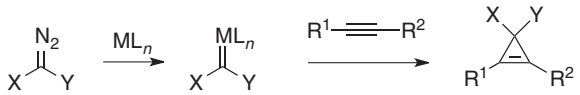


Scheme 83

4.20.5 Addition of Ketocarbenes to Alkynes

4.20.5.1 Intermolecular Reactions

Cyclopropenes are versatile building blocks for a wide array of interesting products. This fact makes them still attractive for the synthetic community. This interest is based on its highly strained structure, which favors transformations that are thermodynamically unfavorable for typical olefins. One of the most general approaches for the synthesis of cyclopropenes involves the reaction of alkynes with metal carbenoids generated from diazo compounds (Scheme 84).



Scheme 84

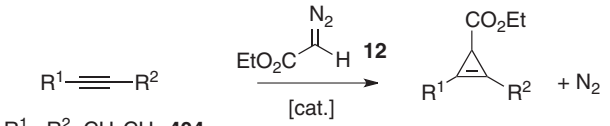
Despite the obvious similarities between both cyclopropanation and cyclopropenation, most efforts have been devoted to the former transformation, the catalytic systems reported to date for the cyclopropenation reaction being reduced to a few, and mainly based on copper and rhodium.

First catalytic systems described were copper, bronze, Cu(I) and Cu(II) salts, but high temperatures (90–140 °C) were required and yields were low.[944] At room temperature, $Rh_2(OAc)_4$ **36** has been the catalyst of choice for this transformation, as reported by Hubert et al.[945]

When studying cyclopropenation from the point of view of the starting alkyne, two groups can be considered, internal or terminal alkynes. Reviewing the literature one may reach the conclusion that rhodium catalysts are preferred for reactions with terminal alkynes, whereas copper catalysts have been extensively used for internal ones.

4.20.5.1.1 Internal alkynes

Most of the studies involving internal alkynes have used acceptor-substituted carbenoids, such as those derived from ethyl diazoacetate **12** due to its higher reactivity. As internal alkynes, 3-hexyne **404** or 1-phenylpropyne **405** have been mostly used in benchmark reactions to determine the activity of several catalytic systems.



R^1= R^2=CH_2CH_3 **404**
or R^1= C_6H_5 and
R^2=CH_3 **405**

(97)

Table 92 gathers the best results published up to now for these reactions.

Table 92 Results in cyclopropenation reactions of 3-hexyne **404** or 1-phenylpropyne **405** with ethyl diazoacetate **12**

Alkyne	*Alkyne/ADE ratio*	*Catalyst*	*Yield (%)*	*References*
3-Hexyne **404**	1.1	Tp^{Cy}-Cu	97	946
	1:1	Tp^{Np}-Cu	84	946
	5:1	$[Ms(CH_2SCN)_3]$-Cu	53	947
	2.5:1	$[PhBP_3]Cu(PPh_3)$	57	364
1-Phenylpropyne **405**	1.1	Tp^{Cy}-Cu	85	364
	5:1	$Cu[Ms(CH_2SCN)_3]$	51	947

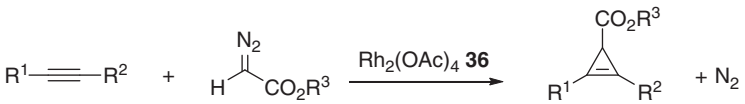
Moderate to high yields have been achieved, the best catalytic system being the one based on TP^xCu **155** complexes. One of the main advantages of these catalysts is that no excess of alkyne is required in order to achieve good yields.[946]

In the case of $[PhBP_3]Cu(PPh_3)$ **407**, in spite of its similarity to TP^xCu **155** complexes lower yields were achieved.[364]

Besides the use of Cu–complexes, $Rh_2(OAc)_4$ **36** has been the selected catalyst for the cyclopropenation of a wide variety of internal alkynes.[945,948–950] The reactions take place smoothly at room temperature, normally with good yields (Table 93).

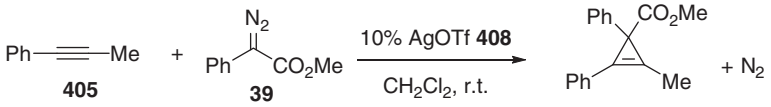
Table 93 Results in cyclopropenation reactions catalyzed by $Rh_2(OAc)_4$ **36**

R^1	R^2	R^3	*Yield (%)*	*References*
C_2H_5	C_2H_5	CH_3	68	945
CH_3OCH_2	CH_3OCH_2	CH_3	38	945
CH_3COOCH_2	CH_3COOCH_2	Et	30	948
–	–	^{t}Bu	65	948
Ph	Et	Et	56	949,950
Ph	Bu	Et	63	949,950
Ph	Me	Et	56	949,950



(98)

The use of substituted donor/acceptor carbenoids has also been described in cyclopropenation reactions of internal alkynes. In this case, traditional catalytic systems based on Cu failed to undergo cyclopropenation reactions. A more reactive carbenoid was needed and just very recently Davies[155] succeded in obtaining highly substituted cyclopropene using silver triflate **408** as catalyst.

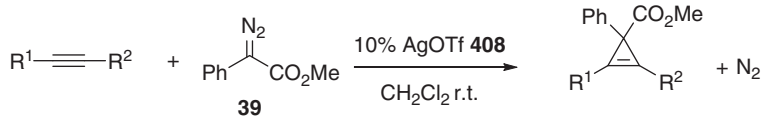


(99)

The generality of the silver-catalyzed cyclopropenation was investigated with a range of disubstituted alkynes, and the cyclopropene products were obtained in good to excellent yields (Table 94).

Table 94 Results of cyclopropenation reactions with **39** catalyzed by AgOTf **408**

R^1	R^2	*Yield (%)*
C_6H_5	CH_3	97
C_6H_5	Bu	93
p-Br-C_6H_5	Bu	82
p-CH_3O-C_6H_5	Bu	68
C_6H_5	C_6H_5–CH_2	91
C_6H_5	C_6H_5	98
C_6H_5	H	0
C_6H_5	TMS	0

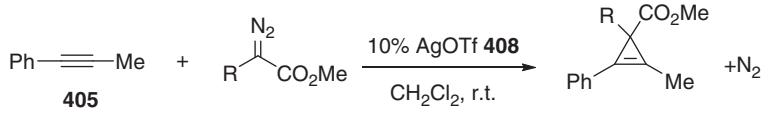


(100)

This catalytic system was also effective with substituted aryl methyldiazoacetates (Table 95).

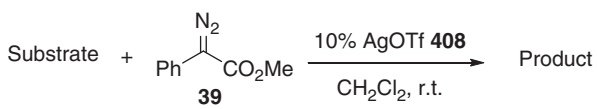
Table 95 Results of cyclopropenation reactions of 1-phenyl-1-butene with aryl methyldiazoacetates catalyzed by AgOTf **408**

R	*Yield (%)*
p-Br-C_6H_5	93
p-TfO-C_6H_5	90
p-^{t}Bu-C_6H_5	82
p-CH_3O-C_6H_5	0



(101)

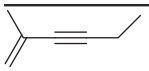
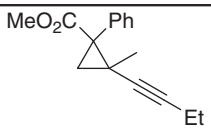
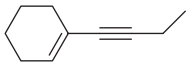
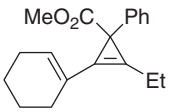
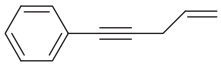
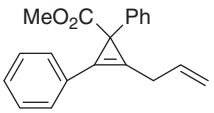
Further studies have been carried out to test the chemoselectivity of AgOTf-catalyzed cyclopropenation reactions. Substrates containing both alkyne and alkene moieties were tested to determine whether cyclopropenation would be favored over cyclopropanation. Results strongly depend on the substitution pattern of the alkene moiety (Table 96).



(102)

Unfortunately silver triflate **408** failed in catalyzing reactions of internal alkynes with acceptor or acceptor/acceptor-substituted carbenoids, such as dimethyl diazomalonate **11** or ethyl diazoacetate **12**.

Table 96 Chemoselectivity in cyclopropenation reactions of internal alkynes with phenyl methyldiazoacetate **39** catalyzed by AgOTf **408**

Substrate	*Product*	*Yield (%)*
		89
		85
		86

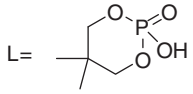
4.20.5.1.2 Terminal alkynes

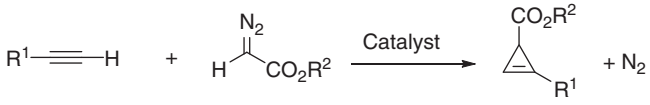
Much more attention has been paid to the cyclopropenation reaction of terminal alkynes. In this case, most of the copper complexes mentioned before failed in carrying out the reaction, except the Tp^x–Cu complexes **155**.

A huge number of publications dealing with cyclopropenation reactions with terminal alkynes used 1-hexyne **409** or phenylacetylene (**14**) as starting products. Acceptor-carbenoids, such as ethyl diazoacetate **12**, has been also preferred for benchmark reactions although other diazo compounds have been also tested for being interesting as precursors of products with biological activity.

The following table shows the most relevant results in cyclopropenation of terminal alkynes (Table 97).

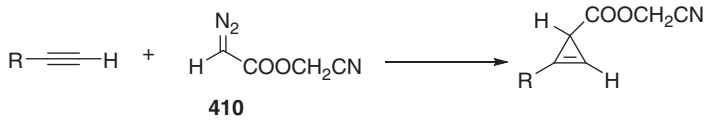
Table 97 Results of cyclopropenation reactions of terminal alkynes

R^1	R^2	*Catalyst*	*Yield (%)*	*References*
Bu	Et	$[Ms(CH_2SCN)_3]$-Cu	32	947
	Et	Tp^{Cy}-Cu **251**	87	946
	Et	$L_2Rh_2(HCO_3)_2$	85	951
	Me		96	951
	Me	$Rh_2(OAc)_4$ **36**	84	945
	Et	$Rh_2(OAc)_4$ **36**	63	950
Ph	Et	$[Ms(CH_2SCN)_3]$-Cu	46	947
Pr	Et	$Rh_2(OAc)_4$ **36**	49	950
C_6H_{13}	Et	$Rh_2(OAc)_4$ **36**	54	950
$Ph(CH_2)_3$	Et	$Rh_2(OAc)_4$ **36**	41	949
$Ph(CH_2)OCH_2$	Et	$Rh_2(OAc)_4$ **36**	18	949
$EtOCH_2$	Et	$Rh_2(OAc)_4$ **36**	No reaction	949



(103)

In some cases more complicated diazo compounds have been selected as carbenoid precursors such as cyanomethyldiazoacetate **410**. The interest of the use of cyanide containing diazoester lies in the structure of some reactive pyrethroid insecticides, which are derivatives of alkenylcyclopropanecarboxylic acid cyanomethyl esters. In this case $Rh_2(OAc)_4$ **36** has been used as catalyst and the desired cyclopropene was obtained in high yields.[137]

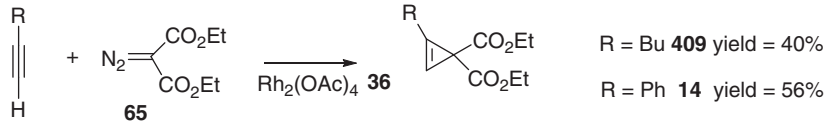


(104)

R = C_3H_7, yield = 85%
R = C_8H_{11}, yield = 80%

Cyclopropenation of 1-hexyne **409** with ethyl nitrodiazoacetate **183** has been carried out by using $Rh_2(OAc)_4$ **36** as a catalyst with 84% yield.[952]

The use of disubstituted diazocompounds provides cyclopropene with a quaternary carbon. Moderate yields have been achieved in the reaction of diethyl diazomalonate **65** with 1-hexyne **409** and 1-phenylacetylene **14** or in the cyclopropenation of 1-hexyne **409** with methyl phenyldiazoacetate **39** catalyzed by $Rh_2(OAc)_4$ **36**.[950]



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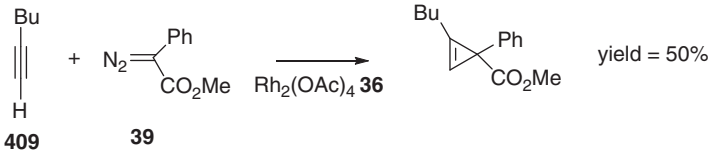
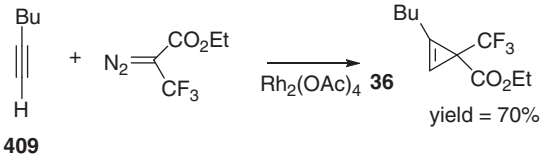


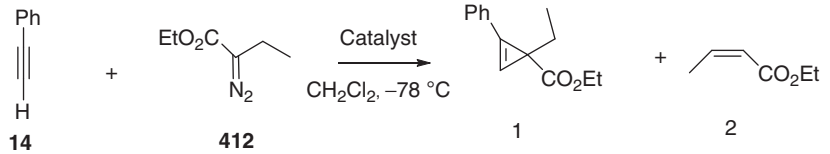
Müller et al.[953] have also described the use of disubstituted diazo compounds bearing a trifluoromethyl group in the cyclopropenation of diphenylacetylene **411** and 1-hexyne **409** catalyzed by $Rh_2(OAc)_4$ **36**. The presence of this fluorinated substituent exerts a profound influence on the biological properties of organic compounds, and are, therefore, of great interest in the pharmaceutical and agrochemical industry.



(106)

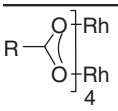
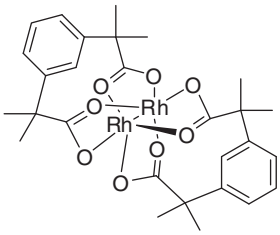
Cyclopropenation reactions have been barely carried out with diazo compounds containing H in the β-position, due to the competition of hydride elimination reaction. Müller[949] and Padwa[954] have presented the first examples In this case, $Rh_2(OAc)_4$ **36** is used as a catalyst in the reaction of 1-hexyne **409** with ethyl α-diazopropionate **412** (44% yield) and α-diazopropiophenone **413** (75% yield), respectively.

More recently Fox et al.[955] have presented the cyclopropenation reaction of phenylacetylene **14** with ethyl diazobutanoate **414**. Several Rh carboxylates and carboxyamidates compounds which had been described as effective catalysts in cyclopropenation reactions with ethyl diazoacetate **12** were surveyed, but most of them (Rh_2(*S*-DOSP)$_4$ **42**, Rh_2(*S*-PTPA)$_4$ **415**, Rh_2(5*S*-MEPY)$_4$ **190**, Rh_2(5*S*-MEOX)$_4$ **370** failed in promoting the reaction with ethyl diazobutanoate **414**. The best results were obtained using a sterically constrained catalyst $Rh_2(piv)_4$ **86** (Table 98).

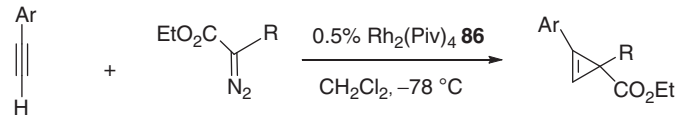


(107)

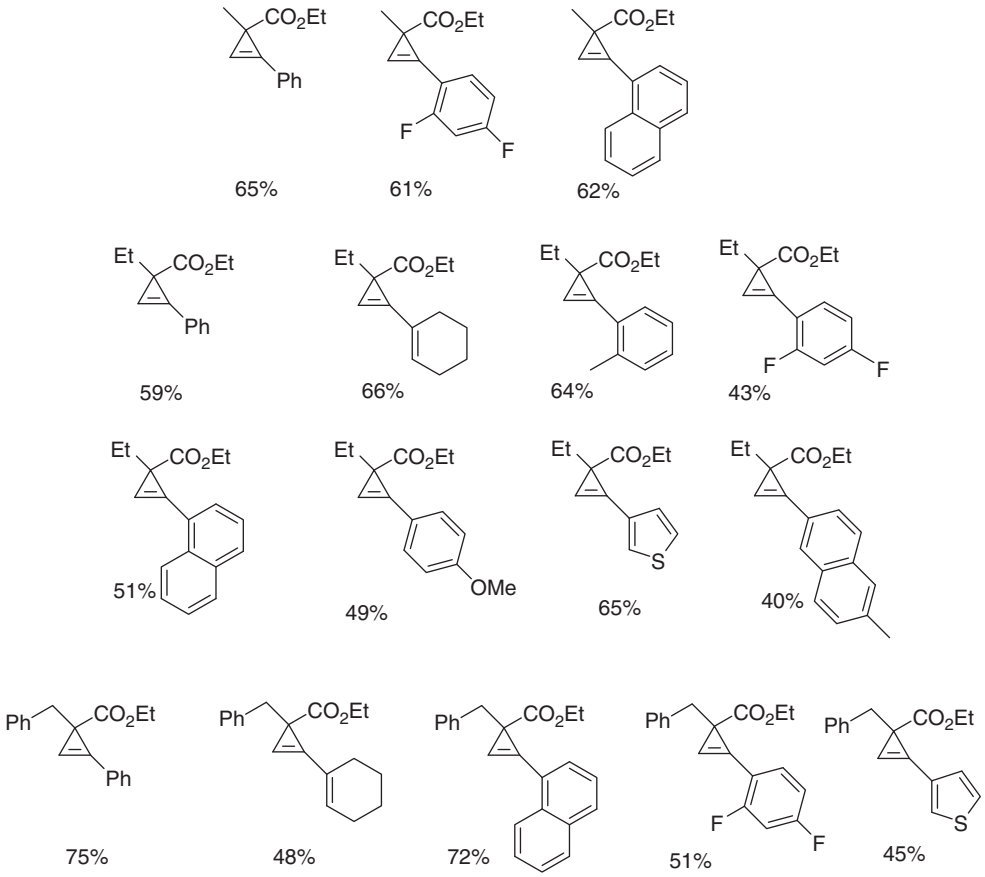
Table 98 Results of cyclopropenation reactions of phenylacetylene **14** with ethyl diazobutanoate **414**

Catalyst	*Yield (%)*	
	1	***2***
		
R = CH_3 ($Rh_2(OAc)_4$) **36**	0	30
R = C_7H_8($Rh_2(Oct)_4$) **83**	6	50
R = CMe_3 ($Rh_2(Piv)_4$) **86**	59	11
R = CMe_2Ph	<5	70
R = $CMePh_2$	58	13
R = Ph_3 (Rh_2TPA_4) **162**	29	40
R = CF_3 (Rh_2TFA_4)	0	80
Rh_2esp_2**71**	44	12
		

The generality of the reaction was tested using several arylacetylene compounds as starting material.



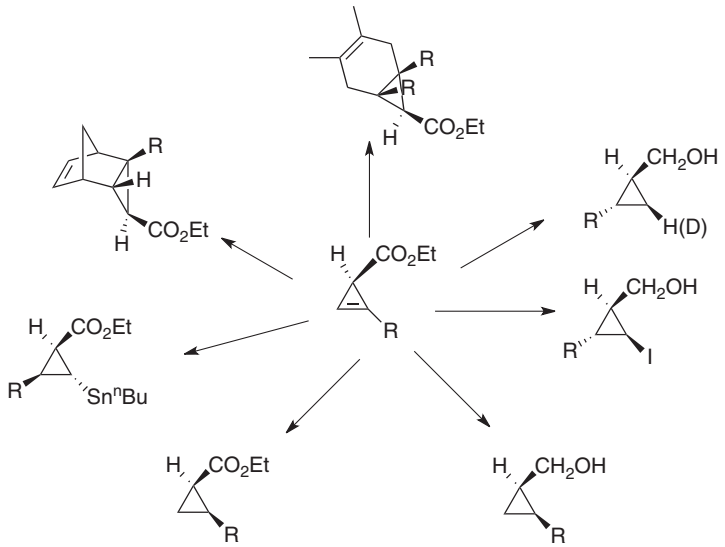
(108)



4.20.5.1.3 Asymmetric cyclopropenation reactions

It has been already mentioned the interest in cyclopropenes as versatile building blocks. When working with enantiomerically enriched cyclopropenes, the transformations result much more interesting, being a route to functionalized chiral compounds.

The following figure gathers some of the classic cyclopropene transformations (Scheme 85).



Scheme 85

First works in this area were presented in the early 1990s[170,956] by Doyle, Müller and coworkers, using dirhodium(II) tetrakis [methyl 2-oxopyrrolidinie-(5*R*)-carboxylate] [Rh_2(*S*-MEPY)$_4$] **190** as catalyst. Since then several catalytic systems, most based on rhodium complexes, but also on iridium, cobalt, or copper, have been studied in asymmetric cyclopropenation reactions. In this case, only the reaction of terminal alkynes have been described, due that most of the catalytic systems gave unsatisfactory results with internal ones.

To describe the most relevant results, start by reviewing cyclopropenation reactions involving ethyl diazoacetate **12** as the acceptor-substituted precursor (Table 99).

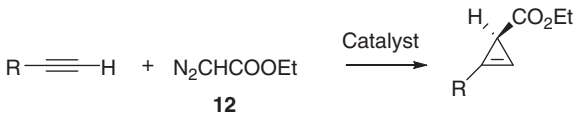
Table 99 Results of cyclopropenation reactions of several terminal alkynes with ethyl diazoacetate **12**

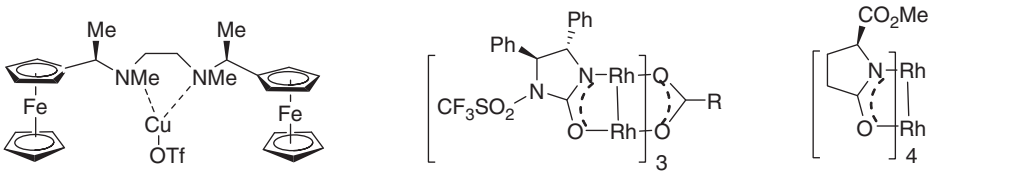
R	*Catalyst*	*Cat. (%)*	*Yield (%)*	ee *(%)*	*References*
Bu^n	Cu bisferrocenyldiamine(OTf)	2.0	68	63	957
Bu^n	[Rh_2{(2*S*)-MEPY}$_4$] **190**	1.0	70	54	288
npent	[Rh_2(OAc)(DPTI)$_3$] **416**	0.5	90	95	848
npent	[Rh_2(OAc)(DPTI)$_3$] **416**	0.05	84	91	536
Ph	Cu bisferrocenyldiamine(OTf)	2	81	68	957
Bu^t	[Rh_2{(5*S*)-MEPY}$_4$] **190**		85	57	288
Bu^t	[Rh_2(OAc)(DPTI)$_3$] **416**	0.05	81	90	536
$BrCH_2$	Cu bisferrocenyldiamine(OTf)	2	60	64	957
$BrCH_2$	[Rh_2{(5*S*)-MEPY}$_4$] **190**	1.0	41	62	958
$BrCH_2$	[Rh_2(OAc)(DPTI)$_3$] **416**	0.5	62	95	848
CH_3OCH_2	[Rh_2{(5*S*)-MEPY}$_4$] **190**	1.0	73	69	848
CH_3OCH_2	[Rh_2(OAc)(DPTI)$_3$] **416**	0.05	78	93	536
$BnOCH_2$	[Rh_2(OAc)(DPTI)$_3$] **416**	0.5	86	92	848
$(CH_3CH_2O)_2CH$	Rh_2{(5*S*)-MEPY}$_4$] **190**	2	85	90	848
$(CH_3CH_2O)_2CH$	[Rh_2(OAc)(DPTI)$_3$] **416**	0.5	64	92	848
$succNCH_2$[a]	Rh_2{(5*S*)- MEPY }$_4$] **190**	2	79	>95	288
$(Ns)_2NCH_2$[b]	Rh_2{(5*S*)-MEPY}$_4$] **190**	2	82	80	288
$(TEOC)_2NCH_2$[c]	Rh_2{(5*S*)-MEPY}$_4$] **190**	2	85	>97	288

[a]succN = succinimido.

[b]$(Ns)_2N$ = *N,N*-di-*para*-nitrophenylsulfonamido.

[c]$(TEOC)_2N$ = *N,N*-di-(2-trimethylsilylethoxycarbonyl)amino.



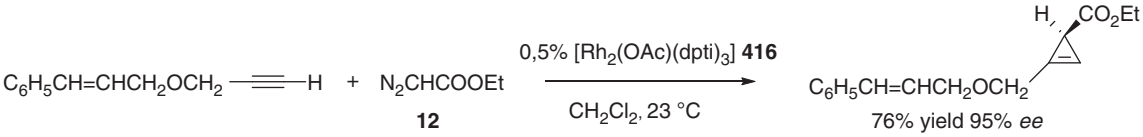


Cu bisferroenyldiamine (OTf) $Rh_2(OAc)(DPTI)_3$ **416** $Rh_2(5S\text{-MEPY})_4$ **190**

(109)

In general, best results have been achieved with Rh complexes. In the case of using $[Rh_2(5S\text{-MEPY})_4]$ **190** as catalyst, an influence of the alkyne substituents in enantioselectivities is observed. The fact that % *ee* values obtained with alkynes bearing substituent containing O or N are higher than those with Bu^n indicates that the polarity of the alkyne seems to play a role in enantioselection.

This effect was not observed with $[Rh_2(OAc)(DPTI)_3]$ **416**, where excellent enantioselectivities are provided regardless of the alkyne substituent. In this case, using $[Rh_2(OAc)(DPTI)_3]$ **416** with an alkyne containing a double bond in the molecule, the cycloaddition of ethyl diazoacetate **12** takes place selectively at the acetylenic linkage.[848]

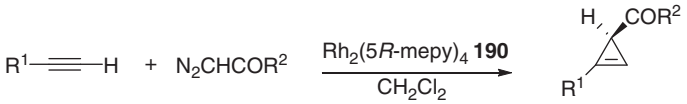


(110)

Doyle et al.[170] carried out a study of the influence of the substituent in the ester group of the diazoacetate in the cyclopropenation reaction of several alkynes using $[Rh_2(5S\text{-MEPY})_4]$ **190** as catalyst. In this case, it is clearly established that the size of the diazocarboxylate substituent plays a critical role in the orientation of the carbene within the chiral catalyst for the addition to the alkyne, and thus in the % *ee* values. This effect is also evident in the reaction yields. An increase in the size substituent provokes a decrease of the yield. In the case of menthyldiazoacetate **144**, intramolecular C–H bond insertion reaction competes with cyclopropenation reaction (Table 100).

Table 100 Effect of the substituent in the ester group of the diazoacetate reagent in cyclopropenations reactions catalyzed by $[Rh_2(5S\text{-MEPY})_4]$ **190**

R_1	R_2	*Yield (%)*	ee *(%)*
Bu^n	EtO **12**	70	54
	Bu^tO **133**	69	53
	NMe_2	49	78
	(1*S*,2*R*,5*S*)-menthyl **144**	46	86
OMe	EtO **12**	73	69
	Bu^tO **133**	56	78
	NMe_2	22	>94
	(1*S*,2*R*,5*S*)-menthyl **144**	45	98



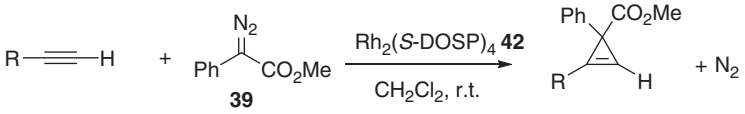
(111)

Davies addressed in 2004 the long-standing problem of preparation of optically active cyclopropenylcarboxylate with a quaternary center via enantioselective cyclopropenation of alkynes. In this case, $Rh_2(S\text{-DOSP})_4$ **42**, was used as catalyst.[959] The catalytic systems described previously such as $[Rh_2(5S\text{-MEPY})_4]$ **190** or $[Rh_2(OAc)(DPTI)_3]$ **416** have been limited thus far to diazoacetates.

The reaction between several alkynes and aryldiazoacetates has been described (Table 101).

Table 101 Results of cyclopropenation reactions of terminal alkynes with methyl phenyldiazoacetate **39** using Rh_2(*S*-DOSP)$_4$ **42** as catalyst

R	*Yield (%)*	ee *(%)*
Ph	62	90
p-Br-C_6H_4	63	92
p-MeO-C_6H_4	67	86
Naphthyl	60	96
p-Et-C_6H_4	48	87
1-Cyclohexenyl	74	92
Bu^n	51	84

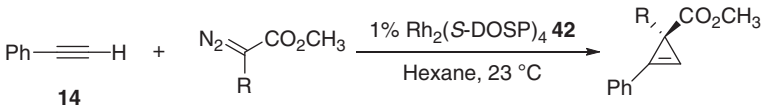


(112)

The study was also extended to the reaction of 1-phenylacetylene **14** and methyl aryldiazoacetates bearing different substituents in the aryl moiety. No influence in the nature of the substituent was observed except for the *p*-MeO derivative. In this case, a lower yield was achieved probably due to the lower reactivity of the carbenoid (Table 102).

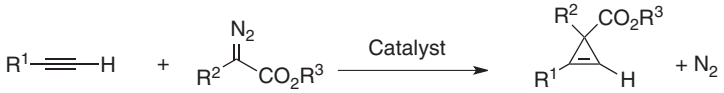
Table 102 Results of cyclopropenation reactions of 1-phenylacetylene **14** with aryl methyldiazoacetates using Rh_2(*S*-DOSP)$_4$ **42** as catalyst

R	*Yield (%)*	ee *(%)*
Ph	62	90
p-Br-C_6H_4	62	86
p-MeO-C_6H_4	24	66
naphtyl	55	86
tiophenyl	57	88
PhCH=CH	0	–



(113)

Since then, other catalytic systems based on rhodium carboxylates and Ir(II)(salen) complexes have been described as efficient catalysts for the cyclopropenation of 1-aryl and 1-alkylacetylenes with methyl alkyl- or aryldiazoacetate reagents (Table 103).[147,159]



(114)

In the case of using [Rh_2(*S*-tbpttl)$_4$] **134** the presence of the 2,3,4-trimethyl-3-pentyl ester moiety (R^3=$(Pr^i)_2CH$) is crucial for high levels of both enantio- and chemoselectivities. Otherwise, no significant effects of the substituents neither in the alkyne nor in the diazo compound (R^2) have been observed.

Ir(II)(salen) **179** and Co(II)(porphirin) **417** catalyst systems have also proved their capability to carry out cyclopropenation reactions with acceptor/acceptor-susbstituted diazo compounds with excellent yields and enantioselectivities.[159,176,207]

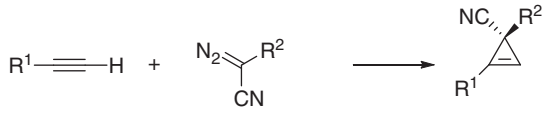
Table 103 Results of cyclopropenation reactions of 1-aryl and 1-alkylalkynes with methyl alkyl or aryldiazoacetate reagents

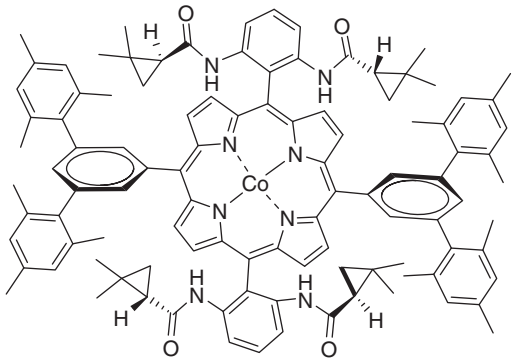
R^1	R^2	R^3	Catalyst	Temperature (°C)	Yield (%)	ee (%)	References
Ph	Me	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	78	95	147
Ph	Me	Et	Rh_2(*S*-tbpttl)$_4$ **134**	–60	25	50	147
Ph	Me	Pr^i	Rh_2(*S*-tbpttl)$_4$ **134**	–60	22	51	147
Ph	Me	Bu^t	Rh_2(*S*-tbpttl)$_4$ **134**	–60	40	96	147
Ph	Pr	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	93	99	147
Ph	Bu	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	84	99	147
p-MeO-C_6H_4	Bu	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	92	98	147
p-Br-C_6H_4	Bu	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	89	98	147
Ph	octyl	$(Pr^i)_2CH$	Rh_2(*S*-tbpttl)$_4$ **134**	–60	85	99	147
n-octyl	Ph	Me	Ir(salen) **179**	–20	96	91	159
Ph	Ph	Me	Ir(salen) **179**	–20	95	96	159
p-MeO-C_6H_4	Ph	Me	Ir(salen) **179**	–20	88	95	159
p-Br-C_6H_4	Ph	Me	Ir(salen) **179**	–20	81	94	159

Carbenoid precursors based on cyanodiazoacetamides and cyanodiazoesters have been used (Table 104).

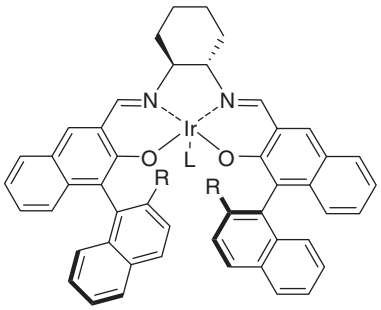
Table 104 Results of cyclopropenation reactions of 1-aryl and 1-alkylacetylenes with several cyanodiazoacetate reagents

R^1	R^2	Catalyst	Yield (%)	ee (%)	References
Ph	CO_2Et	Co(porphirin) **417**	77	93	207
Ph	CO_2Bu^t	Co(porphirin) **417**	76	98	207
Ph	$CONHPr^i$	Co(porphirin) **417**	96	96	207
Ph	$CONMe_2$	Co(porphirin) **417**	95	82	207
Ph	$CONEt_2$	Co(porphirin) **417**	92	80	207
n-octyl	COpirrolidine	Ir(salen) **179**	94	93	159
Ph	COpirrolidine	Ir(salen) **179**	91	94	159
p-MeO-C_6H_4	COpirrolidine	Ir(salen) **179**	97	87	159





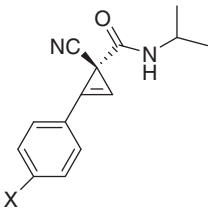
417 [CoP_2]



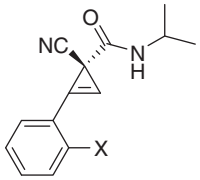
179 [IrSalen, R=C_6H_5, L=(4-CH_3)C_6H_4)]

(115)

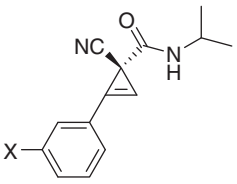
The **417**-catalyzed asymmetric cyclopropenation could be successfully expanded for a wide range of terminal aromatic and related conjugated alkynes in combination with various acceptor/acceptor-substituted diazo reagents.



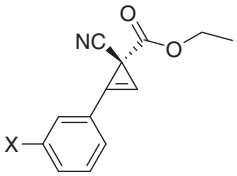
X = Br; 83% yield, 87% *ee*
X = Bu^t; 80% yield, 90% *ee*



X = CH_3; 93% yield, 92% *ee*
X = CHO; 85% yield, 82% *ee*



X = Cl; 75% yield, 99% *ee*
X = F; 50% yield, 98% *ee*
X = OH; 62% yield, 82% *ee*

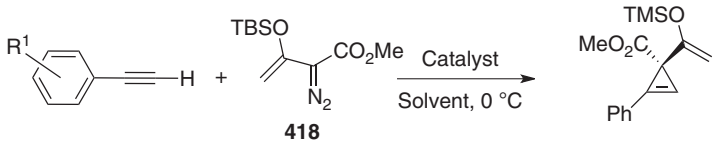


X = OH; 52% yield, 88% *ee*
X = NH_2; 42% yield, 85% *ee*

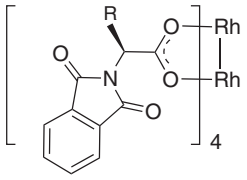
Finally, the cyclopropenation of phenylacetylene **14** with methyl diazoacetoacetate **54** has been described by Davies and Briones[176] using Rh–carboxylate complexes as catalysts. In this case, enantioselectivities below 11% are obtained when the diazoacetoacetate derivative is used. When methyl *tert*-butyldimethylsilyloxyvinyldiazoacetate **418** was addressed as a carbenoid precursor, excellent enantioselectivities were achieved. Subsequent removal of the silylated group with tetrabutylammonium fluoride (TBAF) **419** afforded the cyclopropene with quaternary carbon bearing two acceptor geminal groups. From the study of several rhodium carboxylates, Rh_2(*S*-PTAD)$_4$ **324** appeared as the most effective catalyst in this reaction. The reaction was extended to a great variety of 1-arylalkynes with excellent results (Table 105).

Table 105 Results of cyclopropenation reactions of 1-arylacetylenes with silyloxyvinyldiazoacetate **418**

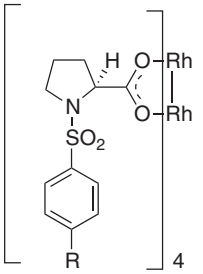
Catalyst	*R^1*	*Solvent*	*Temperature (°C)*	*Yield (%)*	ee *(%)*
Rh_2(*S*-DOSP)$_4$ **42**	H	Pentane	0	41	–51
Rh_2(*S*-BiTISP)$_2$ **140**	H	Pentane	0	43	58
Rh_2(*S*-NTTL)$_4$ **107**	H	CH_2Cl_2	0	93	88
Rh_2(*S*-PTTL)$_4$ **134**	H	CH_2Cl_2	0	91	90
Rh_2(*S*-PTAD)$_4$ **324**	H	CH_2Cl_2	0	93	94
Rh_2(*S*-PTAD)$_4$ **324**	H	CH_2Cl_2	–45	83	98
Rh_2(*S*-PTAD)$_4$ **324**	2-Me	CH_2Cl_2	–45	80	98
Rh_2(*S*-PTAD)$_4$ **324**	4-Me	CH_2Cl_2	–45	86	93
Rh_2(*S*-PTAD)$_4$ **324**	4-Et	CH_2Cl_2	–45	90	97
Rh_2(*S*-PTAD)$_4$ **324**	4-Bu^t	CH_2Cl_2	–45	87	98
Rh_2(*S*-PTAD)$_4$ **324**	4-Br	CH_2Cl_2	–45	92	95
Rh_2(*S*-PTAD)$_4$ **324**	4-Ph	CH_2Cl_2	–45	88	98
Rh_2(*S*-PTAD)$_4$ **324**	3-CF_3	CH_2Cl_2	–45	94	93
Rh_2(*S*-PTAD)$_4$ **324**	2-$CH_2OSiMe_2Bu^t$	CH_2Cl_2	–45	94	99



Catalyst:

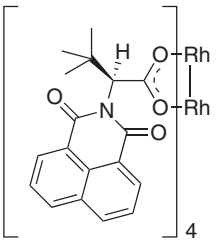


324 Rh_2(*S*-PTAD)$_4$; R= adamantyl
134 Rh_2(*S*-PTTL)$_4$; R=Bu^t

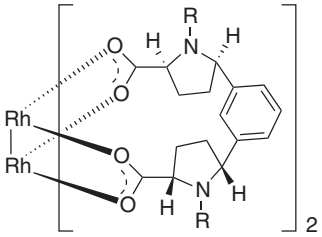


42 Rh_2(*S*-DOSP)$_4$; R=$C_{11}H_{23}$

(116)



107 Rh_2(*S*-NTTL)$_4$

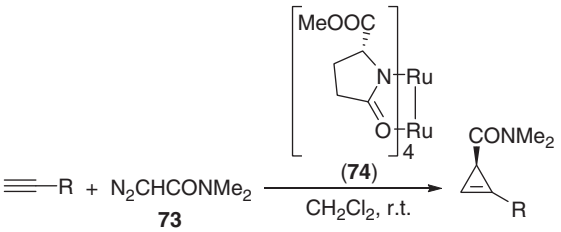


140 Rh_2(*S*-BiTISP)$_2$;R=SO_2-2,4,6-tri$Pr^i C_6H_2$

N,N-dimethyldiazoacetamide **73** has been used in cyclopropanation reactions with a number of alkynes in the presence of Rh_2(5*R*-MEPY)$_4$ **74** to yield the corresponding cyclopropenes with fair yields and high enantioselectivities (equation 117, Table 106).[170]

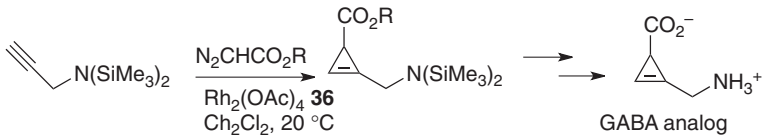
Table 106 Results of some **107**-catalyzed reactions between different alkynes HC≡CR and *N,N*-dimethyldiazoacetamide[170]

R	*Yield (%)*	ee *(%)*
CH_2OMe	22	≥94
Bu	49	78
Bu^t	47	89

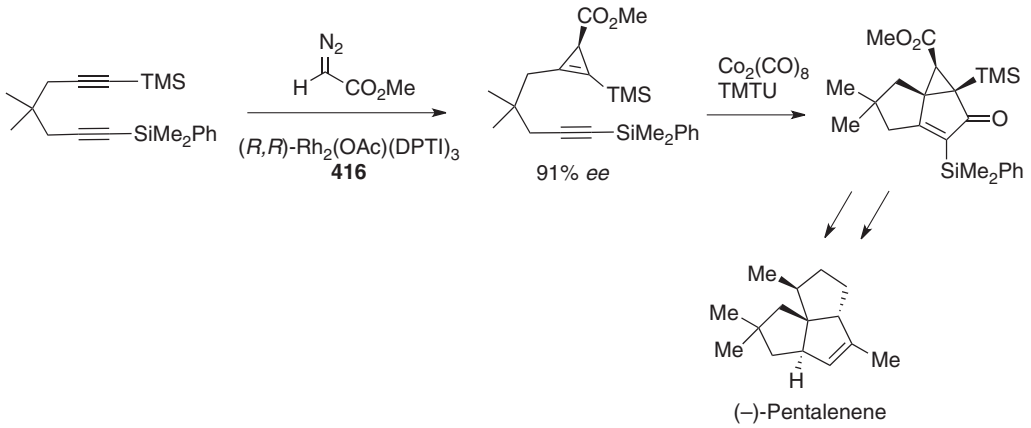


(117)

Cyclopropenation reaction has been used as a crucial step reaction in the synthesis of products of interest such as GABA[960] analogs or in the synthesis of (−)-pentalenene,[961] where the first step is an enantioselective cyclopropenation reaction using Rh_2(OAc)(DPTI)$_3$ **416** as catalyst (Schemes 86 and 87).



Scheme 86

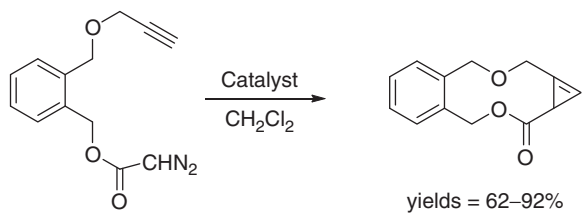


Scheme 87

4.20.5.2 Intramolecular Reactions

There is a growing interest in intramolecular reactions of α-diazocarbonyls containing suitably positioned alkyne functions, which show great potential for the construction of polycyclic molecules from acyclic precursors.

Only one work has been published up to the preparation of this article dealing with intramolecular cyclopropenation reaction with terminal alkynes.[962] In this case, the cyclopropenation, highly dependent on the catalyst, occurred in high yields and enantioselectivities using Rh_2(4-*S*-IBAZ)$_4$ **420** as catalyst.



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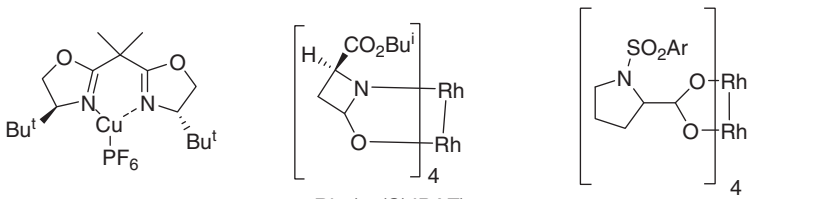
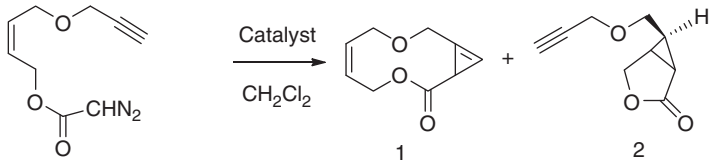


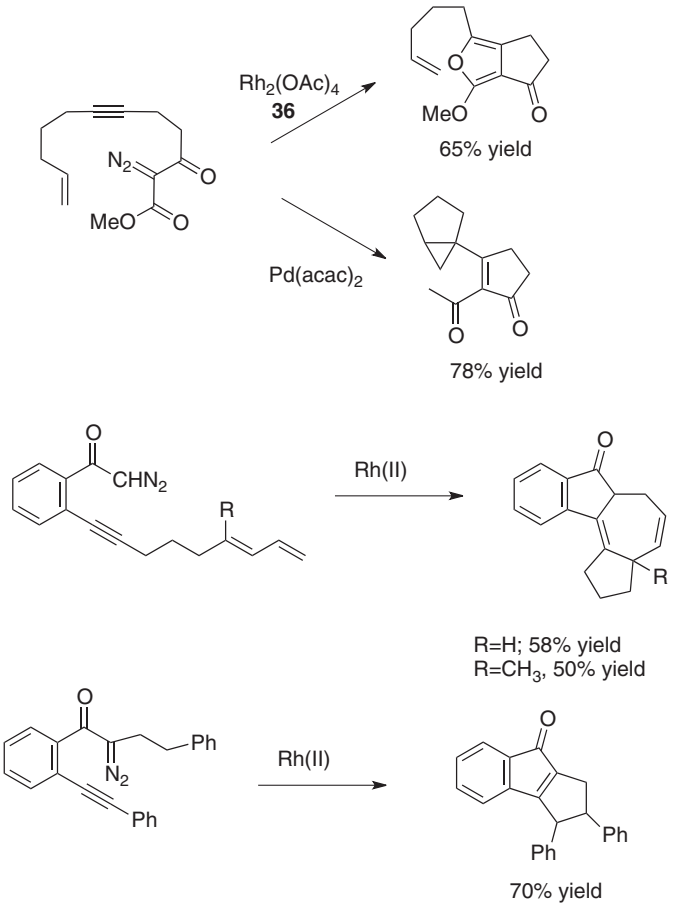


Catalyst	% yield	1:2	% *ee* [1]	% *ee* [2]
$CuBu^tBOXPF_6$	54	31:69	75	–51
420 Rh_2(4-*S*-IBAZ)$_4$	80	4:96	–	96
137 Rh_2(*S*-TBSP)$_4$	87	96:4	12	20

(119)

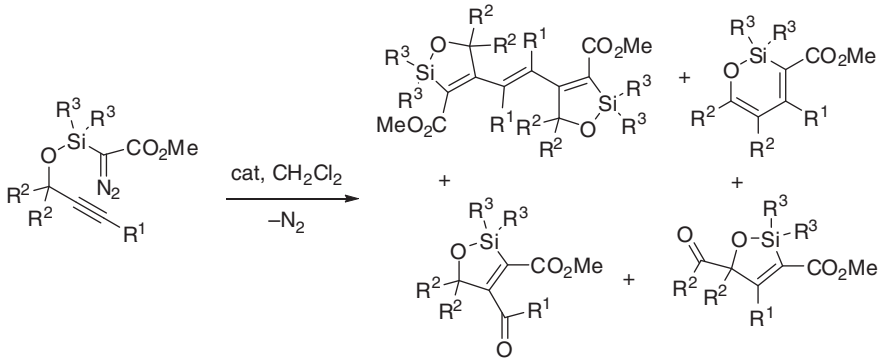
Intramolecular cyclopropenation reactions involving internal alkynes proceed by addition of the rhodium-stabilized carbenoid onto the acetylenic π-bond to give a vinyl carbenoid intermediate. This property has been exploited in tandem reactions. Thus, Padwa et al.[963] have described that the resulting rhodium complex undergoes a wide assortment of reactions including cyclopropanation, 1,2-hydrogen migration, C–H insertion, addition to tethered alkynes, and ylide formation. The exact pathway followed is dependent on the structure of the starting alkyne, the specific metal:ligand ratio employed and is also influenced by the nature of the solvent.

Several examples of the intramolecular processes brought about by vinylcarbenoid intermediates have been beautifully reviewed by McKervey[107] and Padwa.[964] Some of them are gathered in the following figure (**Scheme 88**).



Scheme 88

More recently, Maas and coworkers succeeded in the intramolecular carbenoid reactions of diazoacetates with an alkynyl function tethered to the diazo group by an Si–O link. The reaction was catalyzed by copper(I) triflate **78** and rhodium(II) acetate **36**.[965]



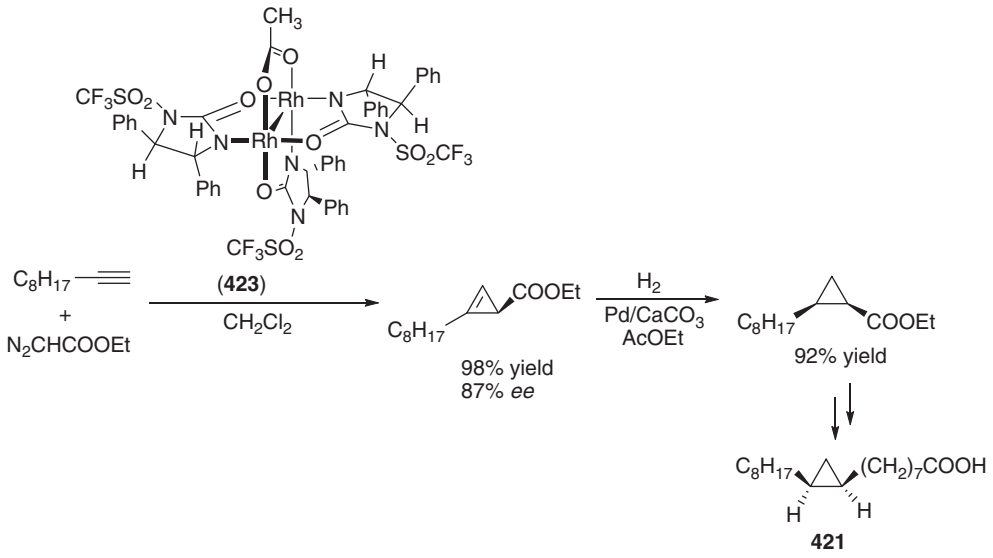
(120)

The proposal of a metal carbene rearrangement from the former diazo carbon atom to the triple bond, together with the possibility of the formation of vinyl cations, has been discussed. Experimental observations pointed toward a metal-mediated intramolecular cyclopropenation and subsequent metal-assisted ring opening of the strained bicyclic cyclopropane, leading to vinylcarbene–metal complexes.

4.20.5.3 Applications of Cyclopropenation Reactions to Total Synthesis

4.20.5.3.1 (9R,10S)-Dihydrosterculic acid

As an alternative method for obtaining a *cis*-cyclopropane, the enantioselective synthesis of a substituted cyclopropene and the subsequent hydrogenation can be carried out. Thus, a catalyzed cyclopropenation reaction has been applied to the enantioselective synthesis of the naturally occurring (9*R*,10*S*)-dihydrosterculic acid **421**, a common fatty acid of microorganisms and subtropical plants. The first step consists of the cyclopropenation of 1-decyne **422** with ethyl diazoacetate **12** in the presence of the Rh catalyst **423** (98% yield, 87% *ee*) (Scheme 89).[848] Thus, subsequent hydrogenation of the resulting cyclopropene afforded the *cis*-substituted cyclopropane (Scheme 89).



Scheme 89

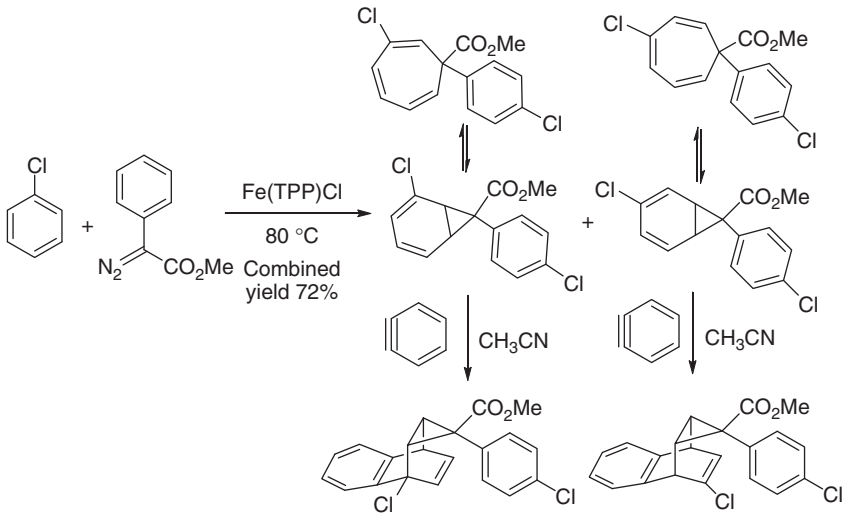
4.20.6 Addition of Ketocarbenoids to Aromatic Systems

4.20.6.1 Benzenes and Other Arenes

Usually the reaction of ketocarbenoids with benzene derivatives leads to cycloheptatrienes following a cyclopropanation/Cope rearrangement tandem process (Buchner reaction).[966] Rh-carboxylates (rhodium trifluoroacetate in many cases) have been

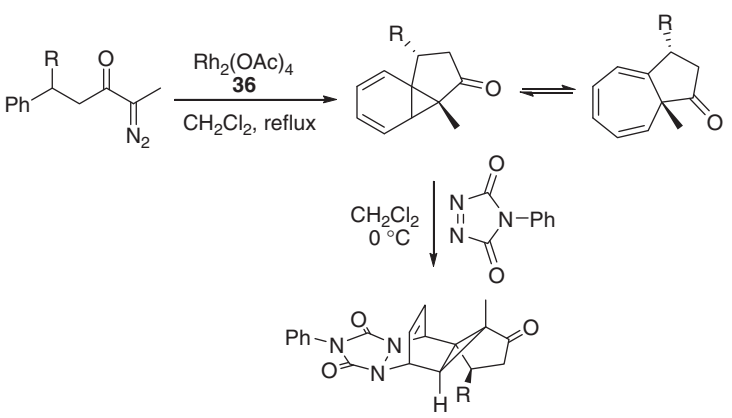
described as the most efficient catalyst for this reaction.[4] Very recently, NHC–Au complexes have been shown to also catalyze this reaction between benzene **424** and ethyl diazoacetate **12**, although in concurrence with the C–H insertion and an electrophilic attack of the metal-carbenoid species has been proposed.[967]

The cyclopropanation/Cope mechanism has been demonstrated by different methods. In some cases the cyclopropane, in fact a norcaradiene, has been trapped by means of Diels–Alder reactions due to its behavior as diene. For example, the norcaradiene obtained in the reaction of toluene **425** and *tert*-butyl diazoacetate **133** has been trapped with fullerene.[454] Chloro(tetraphenylporphyrinato)iron **426** has shown to be active in the Buchner reaction of aryldiazoacetates with different substituted benzenes. Rapidly equilibrating mixture of norcaradiene/cycloheptatriene is obtained in all cases, together with some C–H insertion products obtained by thermal cyclopropane ring opening. The norcaradiene structure has been trapped with benzyne leading to benzhomobarrelene products (Scheme 90).[968]



Scheme 90

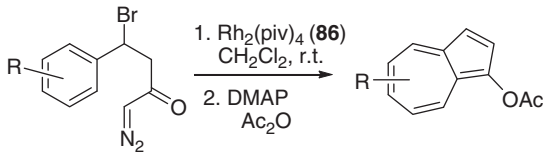
trans-Substituted azulenones have been obtained by intramolecular Buchner reaction of diazoketones with excellent diastereoselectivity. The tautomeric norcaradienes have been also trapped by Diels–Alder reaction with 4-phenyl-1,2,4-triazoline-3,5-dione **427**.[969] In the case of the allyl-substituted ketone, the products of Buchner reaction and cyclopropanation of the allyl group were obtained in nearly the same amount. Methoxy substitution in the benzene ring accelerates the reaction but lowers the diastereoselectivity due to the easier equilibrium between *trans*- and *cis*-azulenones, and even more with the less bulky R substituents (Scheme 91).[970]



R	Yield	*trans:cis*
Et	79%	96:4
Pr	74%	97:3
Pr^i	74%	>98:2
Bu	70%	98:2
Bu^t	72%	>98:2

Scheme 91

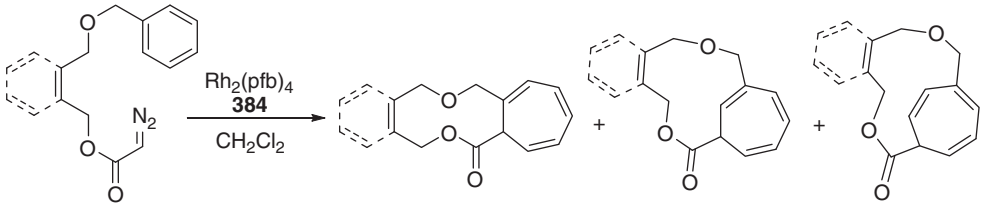
Cyclization of β'-bromo-α-diazoketones catalyzed by rhodium carboxylates, followed by elimination of HBr and trapping, allows the preparation of 1-hydroxyazulene derivatives.[971]



R	Yield
o-Cl	58%
p-Cl	61%
p-Me	47%
p-CN	39%
p-NO_2	21%
m-Br	39%
m-CF_3	40%

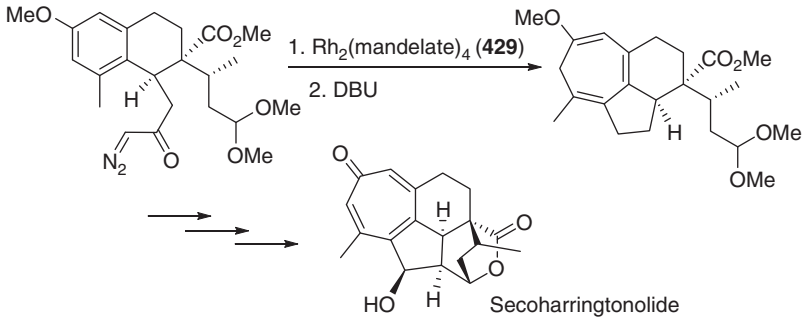
(121)

The intramolecular Buchner reaction of diazoacetates with distal arene rings has been used to obtain macrocycles. Regioselectivity can be an issue, and mixtures of the possible products (attacks in 1,2-, 2,3-, and 3,4-positions) are obtained.[972] $Rh_2(pfb)_4$ **384** must be used, as other Rh catalysts promote the cyclopropanation of the *cis* double bond.



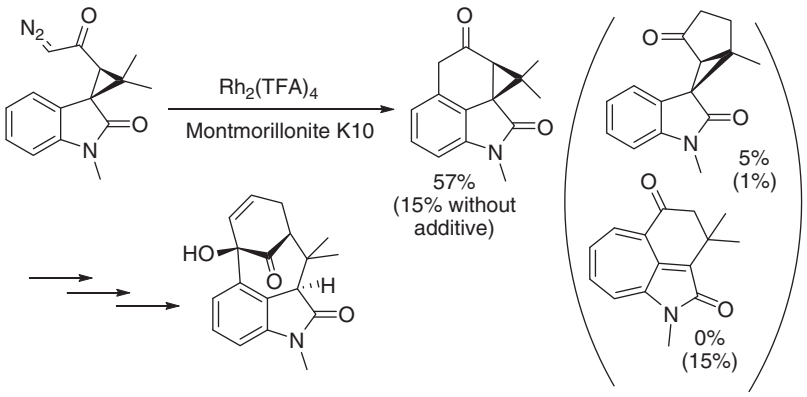
(122)

The intramolecular Buchner reaction catalyzed by $Rh_2(mandelate)_4$ **429** has been used as the key step in the preparation of the polycyclic skeleton of the unusual troponoid diterpene lactone, secoharringtonolide **430** (Scheme 92).[485]



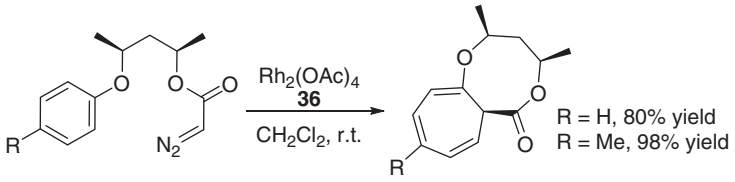
Scheme 92

In some cases, the cycloheptatriene is the undesired product, as the competitive formal C–H insertion is the objective. This is the case of stereoselective construction of the welwitindolinone carbon skeleton. It was shown that the addition of the clay montmorillonite K10 to the reaction medium inhibits the Buchner reaction, allowing the rearrangement of the hypothetic biscyclopropane intermediate to the desired product (Scheme 93).[973]



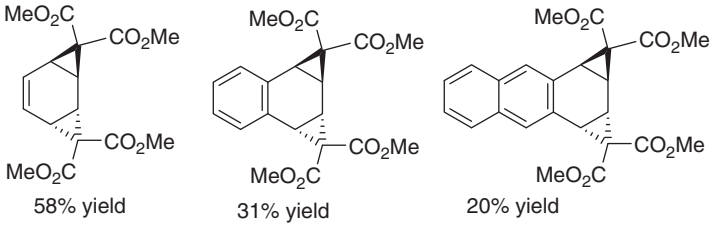
Scheme 93

Optically active tropilidenes can be obtained by intramolecular Buchner reaction of a diazoacetate, linked to the aromatic group by a chiral 2,4-pentanediol tether. 7*S*-tropilidenes were obtained with no traces of the 7*R* enantiomer.[486] The presence of the methyl groups in the chiral tether is crucial to entropically control the stereochemical course of the reaction.[442,460]

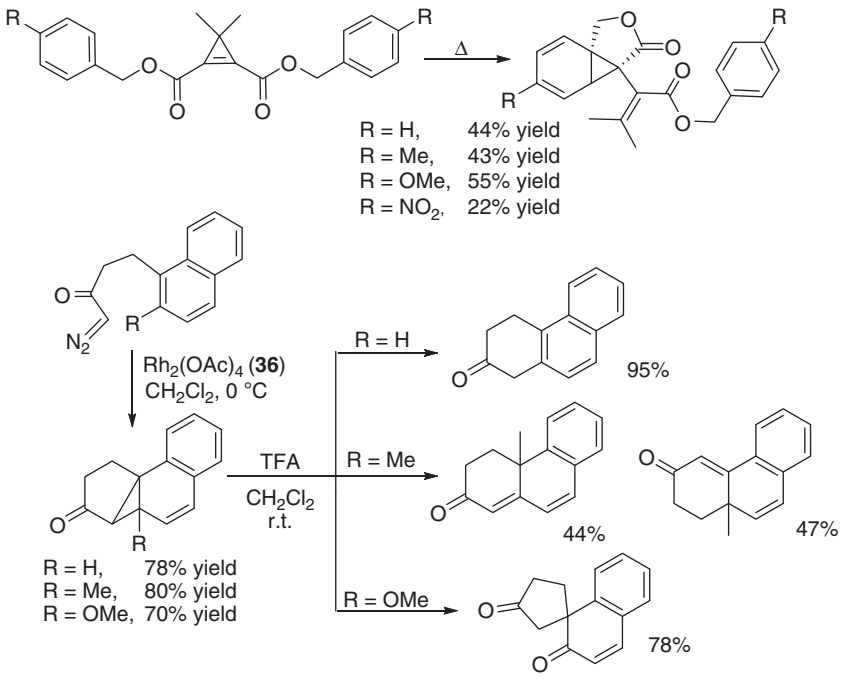


(123)

Depending on the structure of the ketocarbenoid and benzenic compound the cyclopropane can be stable enough to be isolated. For example, the dicyclopropane can be obtained with 58% yield from the reaction of benzene **424** and dimethyl diazomalonate **11** catalyzed by $Rh_2(OAc)_4$ **36**. Analogous dicyclopropanes can be obtained from naphthalene **431** or anthracene **432** albeit in lower yields.[974]

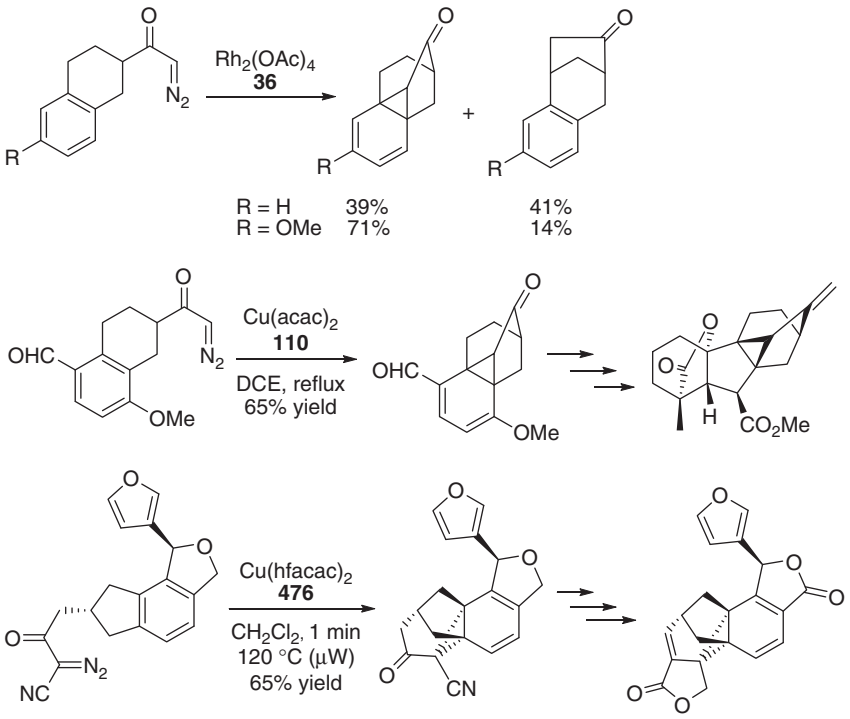


In the case of intramolecular Buchner reactions several types of norcaradienes have been isolated, for example, in the thermal decomposition of a symmetrical cyclopropene,[42] or the cyclization of 1-diazo-4-(naphthyl)butan-2-one **433**.[477] The subsequent evolution of the norcaradiene structure upon acidic treatment depends on the substituents of the starting naphthalene, as they control the relative stability of the carbenium ions and the possible rearrangements. Dihydrophenanthrenones, spiro compounds, and anthracenones are obtained depending on the R group, the position of the side chain in the naphthalene ring, and the presence of additional substituents (Scheme 94).



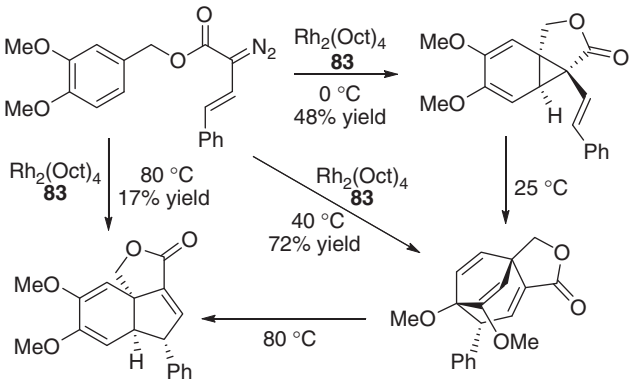
Scheme 94

In other cases, the norcaradienes themselves have interest as intermediates for the synthesis of natural products,[975] for example, in the synthesis of antheridiogens[287,485,976] or salvileucalin B **434**[197,977] (see Section 4.20.6.5.4; Scheme 95).



Scheme 95

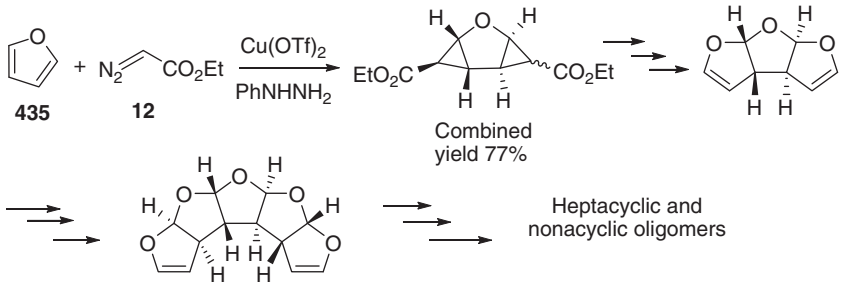
Vinylketocarbenoids may react with benzenes in different ways depending on the reaction conditions. In the intramolecular version, the primary norcaradiene product of cyclopropanation can be isolated at low temperature, whereas the 3+4 product is obtained at 40 °C, presumably by a cyclopropanation/Cope tandem process. At 80 °C, a formal 2+3 cyclization takes place, explained by a vinylcyclopropane rearrangement from norcaradiene, obtained by a retro-Cope rearrangement of the 3+4 product, or directly from this product by a [1,3]-sigmatropic rearrangement (Scheme 96).[457]



Scheme 96

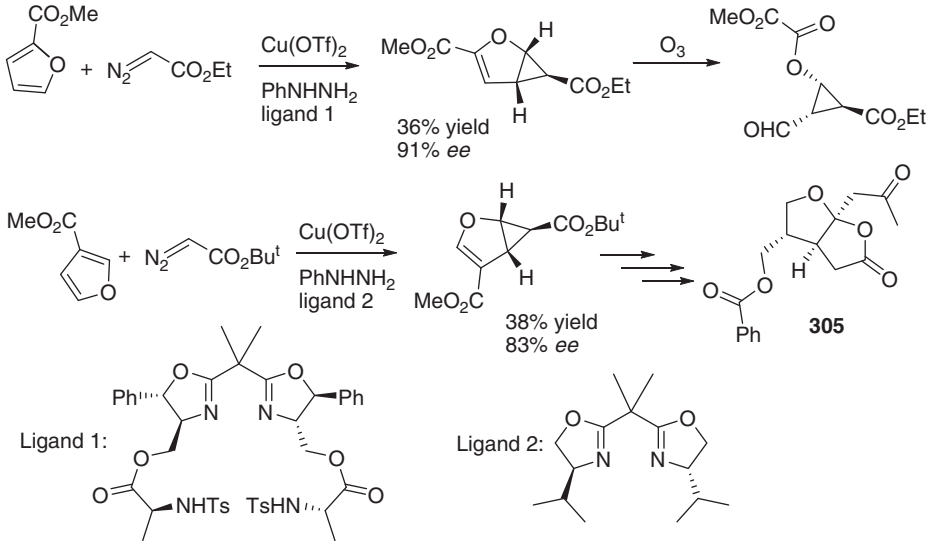
4.20.6.2 Furans

Reaction of furan **435** with ketocarbenoids leads to primary cyclopropanic products, whose stability depends on the type of carbenoid. In general, acceptor-substituted carbenoids, such as ethyl diazoacetate **12**, lead to unstable cyclopropanes. In spite of this, the reaction of **435** and 2,5-dimethylfuran **436** with ethyl diazoacetate **12** catalyzed by $Rh_2(OAc)_4$ **36** allowed the preparation and characterization of the corresponding monocyclopropane and dicyclopropane.[461] A sequence of dicyclopropanation catalyzed by CuOTf **78**, reduction with $LiAlH_4$, and oxidation with 2-iodoxybenzoic acid **437** allows the growth of *anti*-fused oligoannelated THF moieties (Scheme 97).[978]



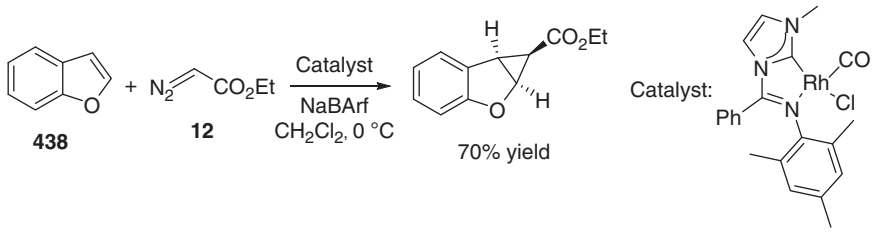
Scheme 97

The stability is higher in the case of cyclopropane from methyl furan-2-carboxylate that has been prepared in enantiopure form, but in modest yield, by copper-catalyzed cyclopropanation using a chiral bis(oxazoline) with secondary binding sites as ligand.[979,980] This bicyclic compound has been used to prepare enantiopure 1,2,3-trisubstituted cyclopropanes. Interestingly, the cyclopropane obtained by the same methodology from methyl furan-3-carboxylate has been used as the starting material for the synthesis of enantiopure (−)-paeonilide (**305**) (Scheme 98).[838]



Scheme 98

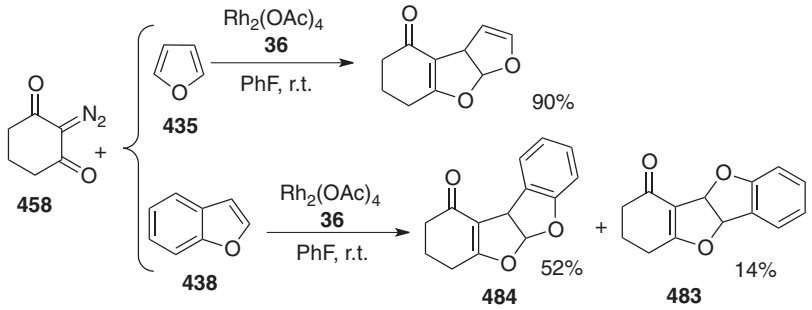
Cyclopropanation is also easier in the case of benzofuran **438**. The *trans*- (or *exo*) cyclopropane is commonly obtained, for example, with $Rh_2(OAc)_4$ **36**, but very recently it has been described in the case of a monomeric imine–Rh–NHC complex that promotes the cyclopropanation of **438** with ethyl diazoacetate **12** with total *cis* (or *endo*) diastereoselectivity.[752]



(124)

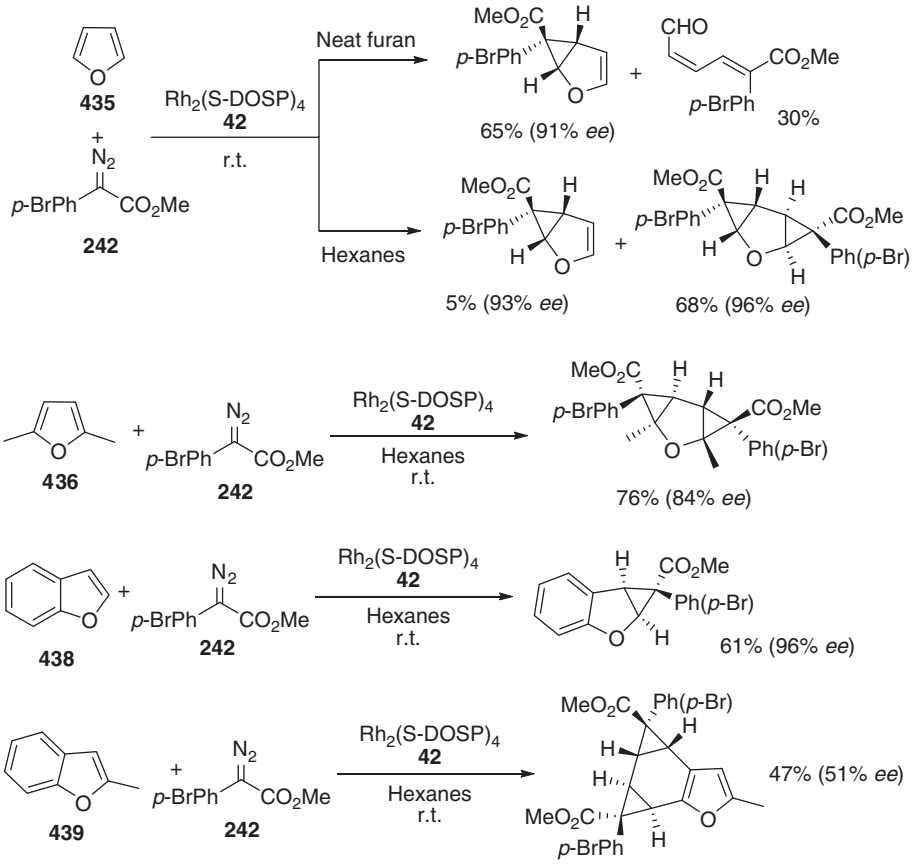
The reaction of **435** and differently substituted furans with an acceptor–acceptor-substituted carbenoid, such as 2-diazocyclohexane-1,3-dione **458** leads to a tricyclic structure, with yield and regioselectivity depending on the substitution at the furan ring. For example, the other regioisomer is obtained as a minor product in a 1:2–3.7 ratio (**483**/**484**) in the case of **438**. The origin of this kind of compounds is not clear, although a cyclopropanation/ring-opening sequence leading to zwitterionic intermediates has been proposed (Scheme 99).[981]

Cyclopropanes are more easily obtained when donor–acceptor carbenoids are used. Reaction of furans and methyl *p*-bromophenyldiazoacetate **242** catalyzed by $Rh_2(S\text{-DOSP})_4$ **42** leads to mono- or bicyclopropanes in almost enantiopure forms.



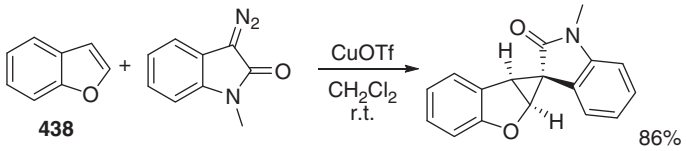
Scheme 99

The stereochemical course of the reaction shows interesting features, as the opposite sense of the chiral induction with the same catalyst in the cyclopropanation of **435** and **436**. The steric role of methyl groups in the approach of **435** to the carbenic carbon has been proposed as a plausible explanation.[515] High enantioselectivity is also obtained in the cyclopropanation of **438** or 3-methylbenzofuran, but in the case of 2-methylbenzofuran **439** double cyclopropanation takes place in the benzene ring with moderate to low enantioselectivity (Scheme 100).



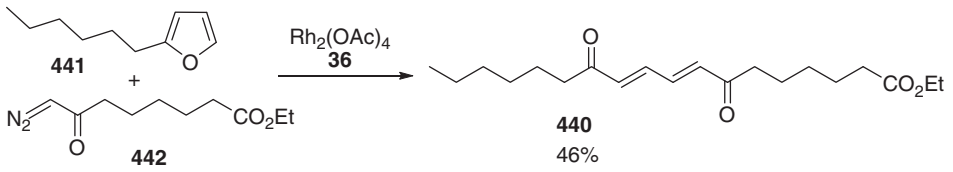
Scheme 100

Spirocyclopropanes have been obtained in the copper-catalyzed reaction of 3-diazo-2-oxoindoles with **438**.[174]



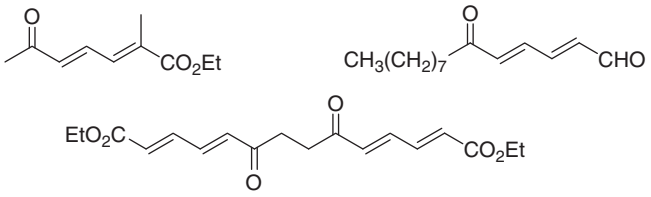
(125)

As mentioned above, the addition of ketocarbenoids to furans leads usually to ring-opening products, in general functionalized dienes, as a consequence of the evolution of the poorly stable cyclopropane and/or the formation of zwitterionic intermediates. The diene keeps an *Z* configuration in the double bond coming from the furan ring and a mixture of *Z* and *E* configurations in the newly created double bond. Isomerization with iodine allows the two-step one-pot synthesis of the *E,E* diene. An example is the synthesis of ostopanic acid **440** from 2-hexylfuran **441** and ethyl 8-diazo-7-ketooctanoate **442**, catalyzed by $Rh_2(OAc)_4$ **36**[982] (see Section 4.20.6.5.1).

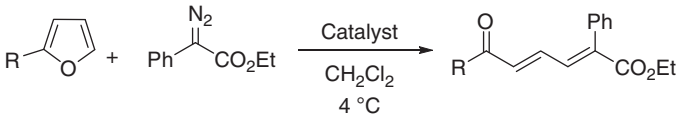


(126)

In the same way, several fragments of retinol/carotene (2-methylfuran **443** and ethyl *α*-diazopropionate **412**), leukotriene (furan **435** and 1-diazo-2-decanone **444**), and corticrocin (1,2-bis(2-furyl)ethane **445** and ethyl diazoacetate **12**) have been prepared.[983]



Excellent yields of the dienes have been obtained in the reaction of aryldiazoacetates with 2-methoxy- or 2-alkylfuran using pentacarbonyl(η^2-*cis*-cyclooctene)chromium(0) (**446**) as a catalyst.[688] Trispyrazolylborate–copper(I) complexes have been described as an interesting alternative to $Rh_2(OAc)_4$ **36** for the addition of **12** to furans.[984]

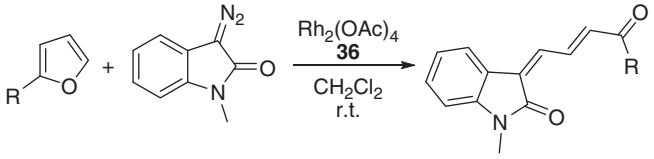


R	Yield
Me	78%
Et	72%
OMe	98%

(127)

catalyst: pentacarbonyl(η^2-*cis*-cyclooctene)chromium(0) (**446**)

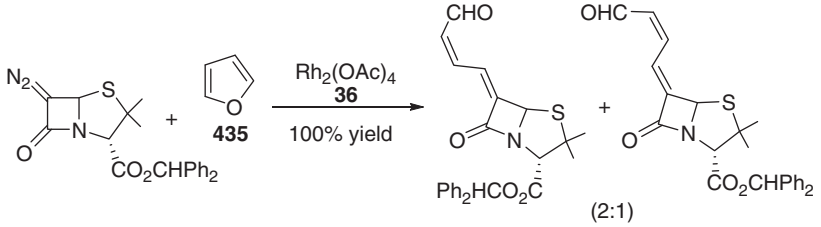
In the reaction of 3-diazo-2-oxoindoles with substituted furans, the expected dienic products are obtained with high regio- (in the case of unsymmetrical furans) and diastereoselectivity.[985]



R	Yield
H	91%
Me	89%
OMe	85%

(128)

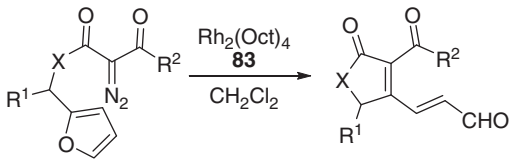
An analogous reaction had been described for 6-diazopenicillates and differently substituted furans. A mixture of two dienals was obtained from the attack to the less substituted position 2 of furan **435**, with *Z* configuration in the C=C obtained from furan, that can be isomerized to the *E* configuration by treatment with silica. In contrast, reaction with benzofuran **438** leads to a spirochromene, albeit in low yield.[986]



(129)

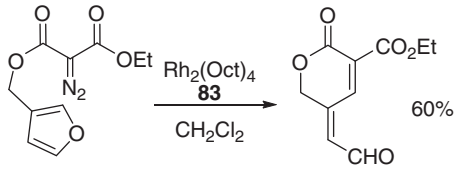
(130)

The intramolecular additions of acceptor–acceptor carbenoids on furans lead to dienic systems included into cycles, five-membered from 2-substituted furans and six-membered from 3-substituted furans. In the first case cyclopentenones with most of the functionality required for prostaglandine synthesis can be obtained. The presence of the terminal ketone instead of an ester promotes a formal 3+2 cycloaddition with formation of a tricyclic structure, the only product in the case of ketoesters, and only the minor product in the case of diketone.[987]

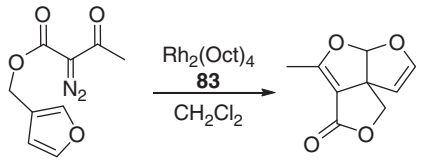


X	R1	R2	Yield
O	H	Me	64%
O	H	OEt	75%
CH_2	OTBS	OMe	75%

(131)



(132)



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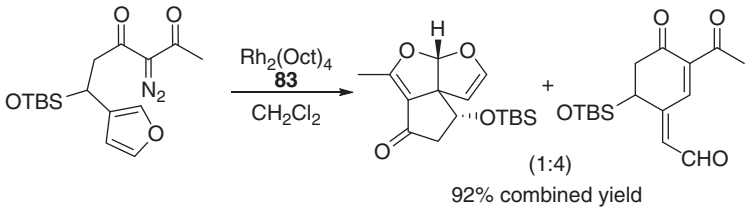
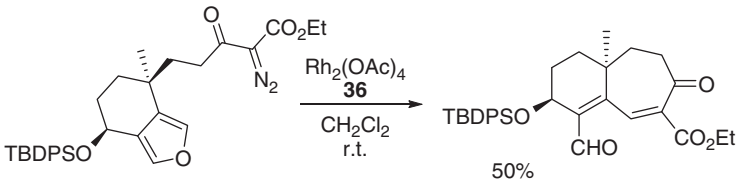


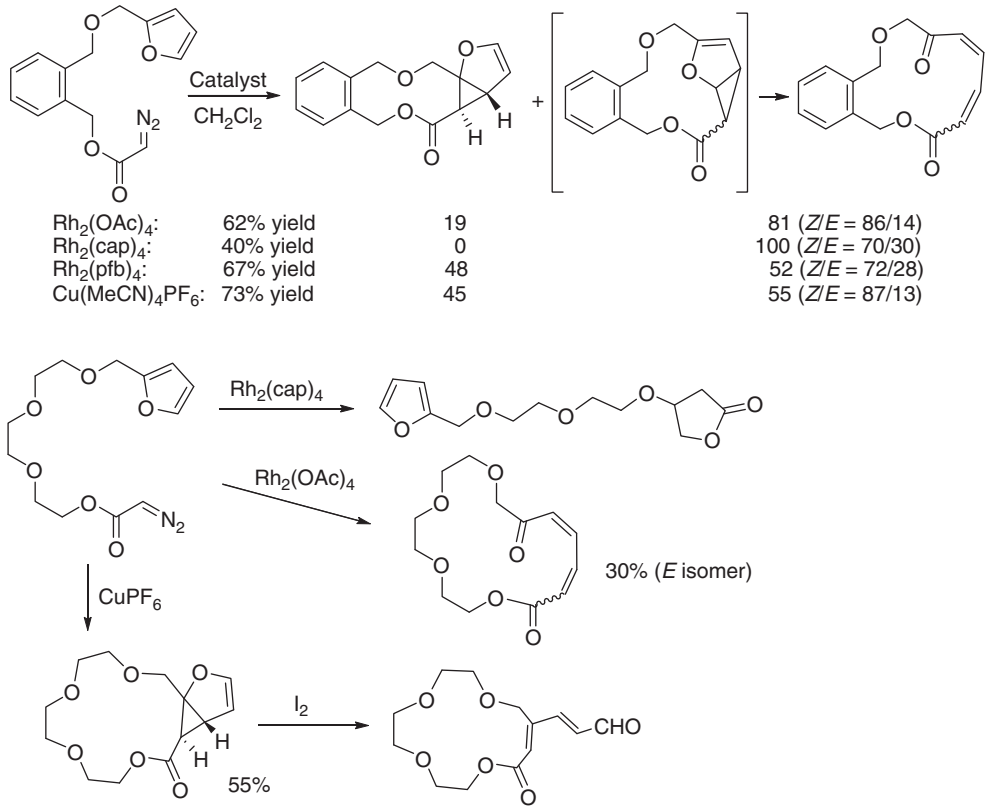
(134)

This strategy has been also tested in the synthesis of guanacastepenes by cyclization of a diazoketoester and opening of the polycyclic intermediate structure, leading to the desired unsaturated system.[988]



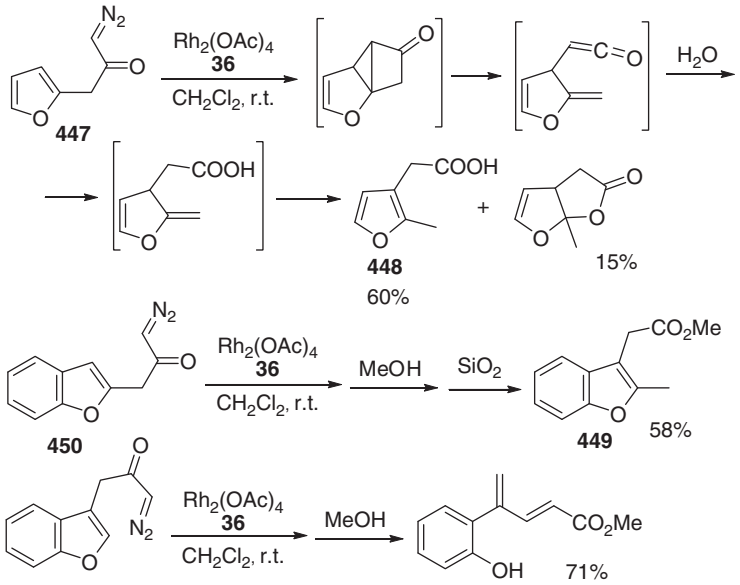
(135)

The intramolecular reaction of furan-substituted diazoacetates has been used for the synthesis of unsaturated macrocyclic lactones. Owing the long chain of the substituent, cyclopropanation can take place on both furan double bonds. In case of reaction at the same side, the resulting cyclopropane is quite stable and can be isolated. The cyclopropane at the opposite side is not stable and leads to the expected diene.[498] The type of catalyst (Cu or Rh) and the ligand (acetate, caprolactamate, and perfluorobutyrate) controls the ratio between the two types of products (Scheme 101).



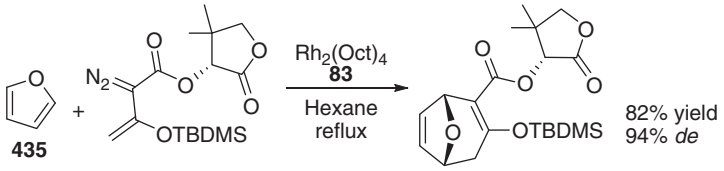
Scheme 101

The reaction of 1-diazo-3-(furan-2-yl)-2-propanone **447** with $Rh_2(OAc)_4$ **36** did not lead to any intramolecular product, only to insertion in benzene solvent,[989] but the result was completely different when water was introduced in the reaction medium. The main product was then (2-methylfuran-3-yl)acetic acid **448**, as a result of a vinylogous Wolff rearrangement of the intermediate cyclopropane, trapping of the formed vinyl ketene and rearomatization. In the same way, methyl (2-methylbenzofuran-3-yl) acetate **449** was obtained from 1-diazo-3-(benzofuran-2-yl)-2-propanone **450** by methanol addition to the reaction medium.[464] The same mechanism works with 3-substituted benzofuran but in that case the evolution of the trapped ketene leads to a phenolic diene by ring opening (Scheme 102).



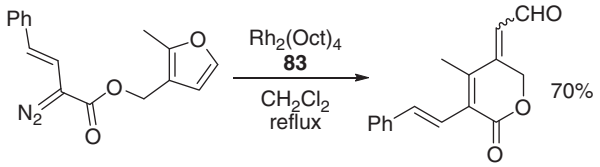
Scheme 102

With vinylketocarbenoids, the tandem cyclopropanation/Cope rearrangement leads to a formal 3+4 cycloaddition with 8-oxabicyclo[3.2.1]octene derivatives as final products. The presence of a chiral auxiliary (lactate **286** and pantolactone **287**) in the ketocarbenoid allows obtaining a high diastereoselectivity, whereas the chiral rhodium catalyst $Rh_2(TBSP)_4$ **137** leads only to moderate enantioselectivity.[509] Trifluromethylated bicyclic compounds have been also obtained in racemic form.[447]

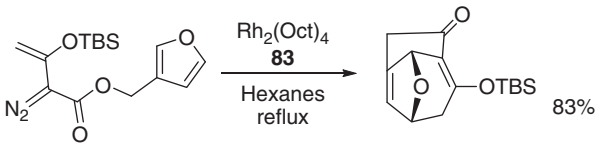


(136)

The intramolecular reaction of vinylketocarbenoids with furans also gives different products depending on the substitution in the vinyl moiety. An unstable triene with a six-membered lactone is obtained from the phenylvinyldiazoacetate, following the usual reaction pathway of ketocarbenoids without vinyl substitution, whereas silyloxyvinyldiazoacetates and diazoketones lead to bicyclic products through [3+4] cycloaddition.[990]



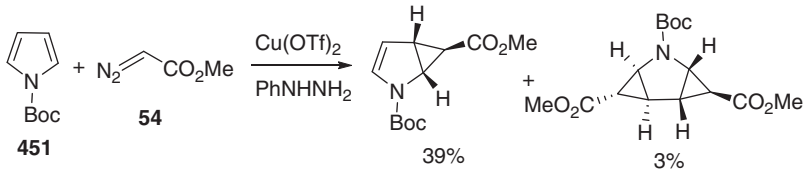
(137)



(138)

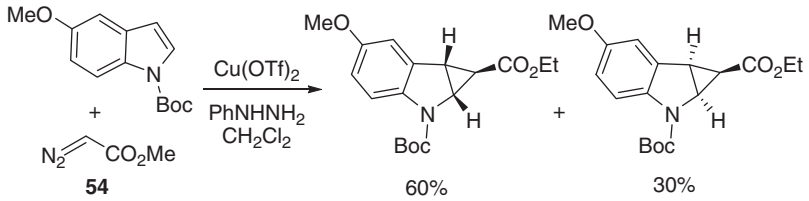
4.20.6.3 Pyrroles and Indoles

Depending on *N*-substitution, pyrroles can undergo different types of reactions with ketocarbenoids. In general *N*-acylpyrroles behave as dienes and are prone to cyclopropanation reactions, whereas *N*-alkylpyrroles or *N*-unsubstituted ones tend to react through zwitterionic intermediates leading insertion products. Cyclopropanation of *N*-Boc-pyrrole **451** proceeds with moderate yield by using the $Cu(OTf)_2/PhNHNH_2$ catalytic system.[991] Only moderate enantioselectivity has been obtained in this reaction with chiral bis(oxazoline) ligands, in contrast with the excellent results obtained with methyl furan-2-carboxylate **452**.[980] The absence of a group for the secondary interaction (H-bond) may account for this difference.



(139)

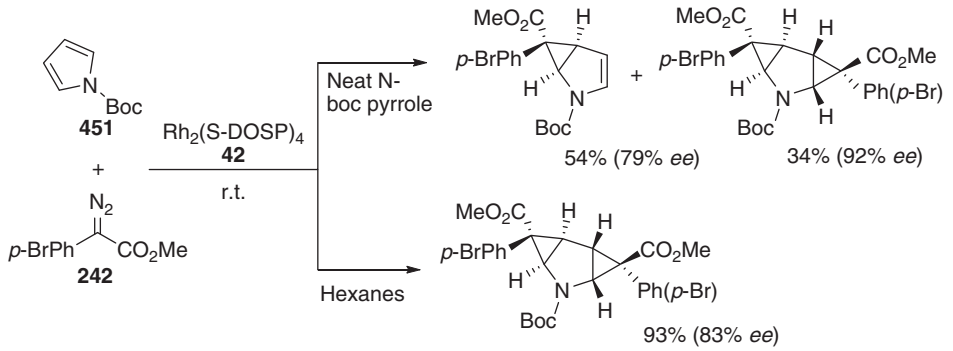
The same method has been used for cyclopropanation of *N*-Boc-indoles with better yield, but the mixture of the two possible stereoisomer was obtained.[992]



(140)

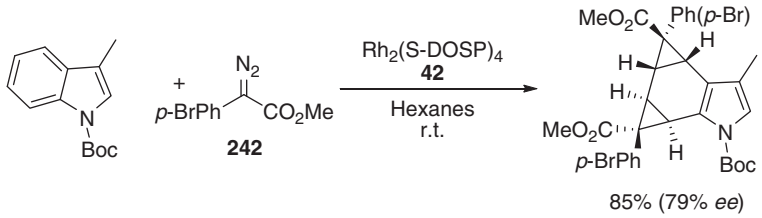
Cyclopropanation is easier with donor–acceptor carbenoids. The dicyclopropane of methyl*p*-bromophenyldiazoacetate **242** can be obtained in high yield and with high enantioselectivity by using $Rh_2(S\text{-}DOSP)_4$ **42** as catalyst. The monocyclopropane is

more difficult to obtain, and *N*-Boc-pyrrole **451** must be used as a solvent and enantioselectivity is not so good. The sense of chiral induction is the opposite to that observed with furan **435**, and the proposed explanation is based on the steric effect of the Boc group (Scheme 103).[515]

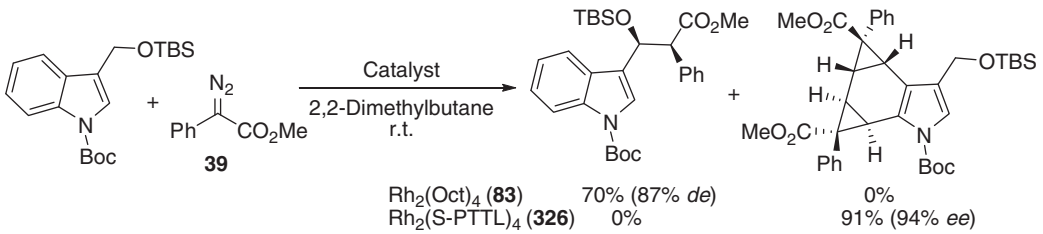


Scheme 103

Cyclopropanation of *N*-Boc-indoles with **242** catalyzed by **42** only takes place when the indole is substituted in position 2 or 3. In this case, the dicyclopropane in the benzenoid ring is obtained in high yield and enantioselectivity.[515] In case that substituent has a position susceptible of C–H insertion, it is necessary to change the rhodium catalyst to Rh_2(*S*-PTTL)$_4$ **326** to obtain total chemoselectivity to cyclopropanation with excellent enantioselectivity.

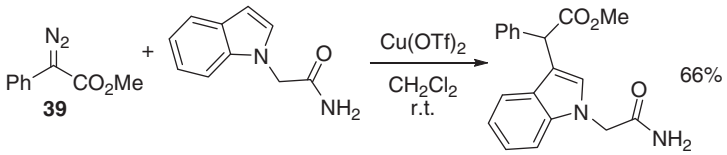


(141)

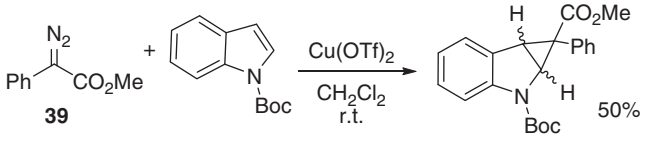


(142)

The difference in reactivity between *N*-alkyl- and *N*-acyl-indoles is also clear in the copper-catalyzed reaction with methyl phenyldiazoacetate **39**, leading to insertion in position 3 or cyclopropanes, respectively.[993] Analogous results have been obtained with other aryldiazoacetates.

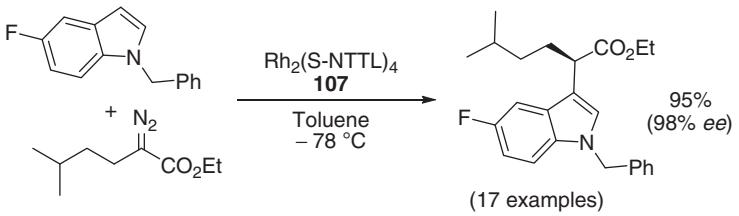


(143)



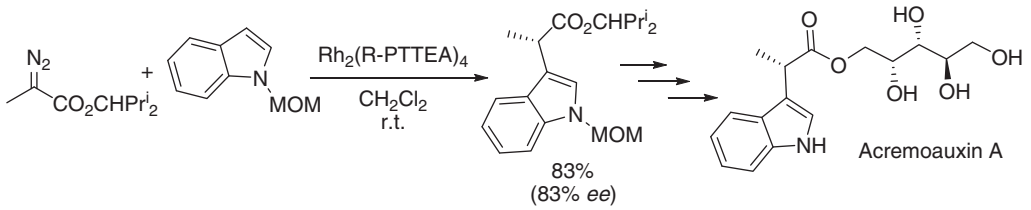
(144)

The reaction of alkyldiazoacetates with indoles catalyzed by rhodium complexes shows an orientation toward insertion in position 3 with high yield and enantioselectivity in the case of **107**. A mechanism through an ylide intermediate is proposed for this reaction instead of the classical cyclopropanation+ring opening.[530]



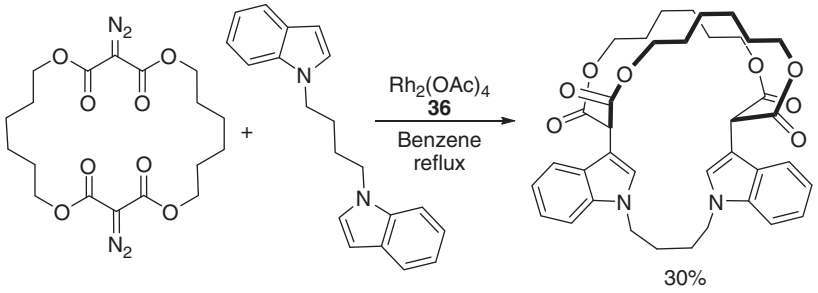
(145)

This strategy has been used for the synthesis of a fragment of acremoauxin A from an *N*-protected indole and a diazopropionate, although the enantioselectivity with this diazo compound is slightly lower than that obtained with others bearing larger substituents (**Scheme 104**).[994]



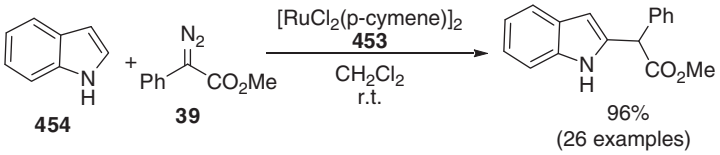
Scheme 104

Diazocompounds derived from macrocyclic malonic derivatives of tri-, tetra-, penta-, and hexa(ethylene glycol) undergo insertion in indanes catalyzed by $Rh_2(OAc)_4$ **36**, leading to 3-indolyl macrocyclic lactones and cryptands.[995]



(146)

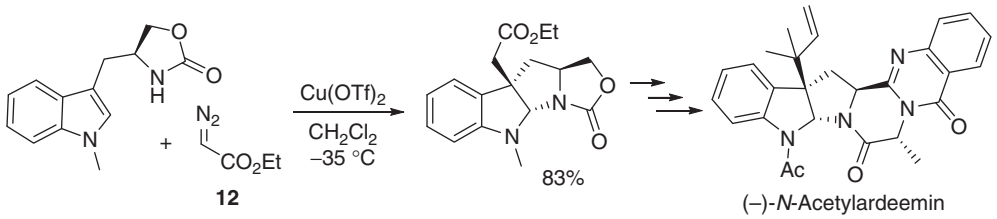
When $[RuCl_2(p\text{-cymene})]_2$ **453** is used as a catalyst, reaction of indole **454** with aryldiazoacetates leads only to insertion products in position 2. The same effect is observed in the reaction with pyrrole **455**.[996]



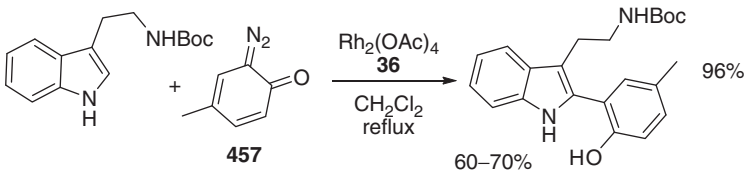
(147)

In the case of reaction of indoles with **12**, the presence of a substituent containing an amide group in position 3 controls the opening of the intermediate cyclopropane. The nitrogen attacks the indolenium cation with amination of position 2 of indole and formation of a tricyclic structure. When the amide is an oxazolidinone, a tetracyclic structure is obtained,[997] a method that has been applied to the total synthesis of (−)-ardeemin **456**[998] (see Section 4.20.6.5.4) and other alkaloids (**Scheme 105**).[868]

This type of cyclization is not observed when 6-diazo-4-methylcyclohexa-2,4-dienone (**457**) is made to react with an indole with an amide containing a substituent. Simple insertion is always observed, with the orientation of the opening modulated by the substitution pattern of the starting indole.[475]

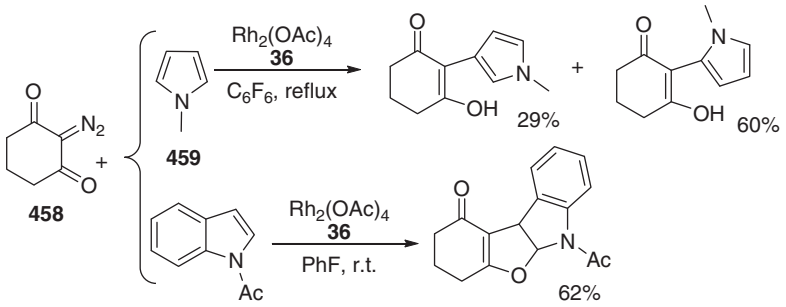


Scheme 105



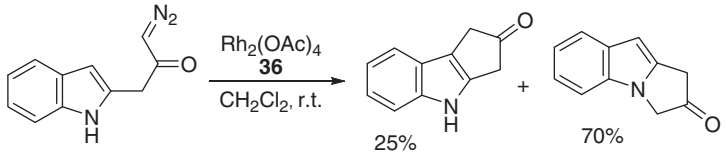
(148)

The reaction of an acceptor–acceptor-substituted carbenoid, such as 2-diazocyclohexane-1,3-dione **458**, with *N*-acyl-pyrroles and indoles leads to the same tricyclic structure described for furans, but with no traces for the other possible regioisomer. On the contrary *N*-methylpyrrole **459** reacts to produce C–H insertion products in both 2 and 3 positions (2:1 ratio) (**Scheme 106**).[981]

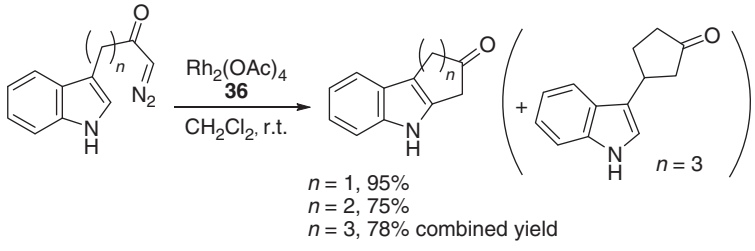


Scheme 106

Intramolecular reactions of diazoketones, although proceeding presumably through an intermediate cyclopropane, lead to C–H insertion products. Side reactions are aliphatic C–H insertion in case of long-chain substituents or cyclization through the nitrogen atom in the case of a diazosubstituent in position 2 of the *N*-unprotected indole.[999]

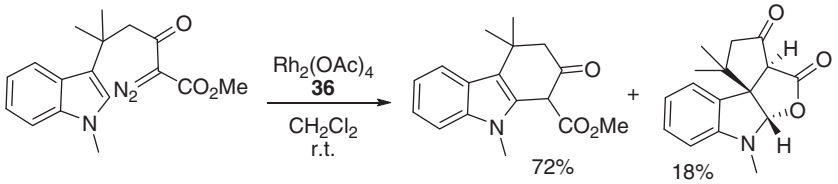


(149)



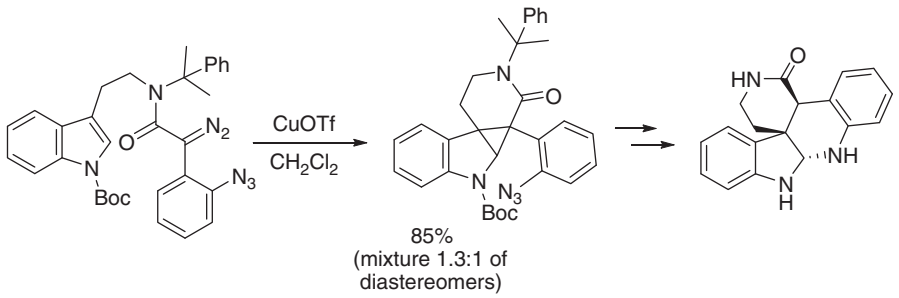
(150)

When the side chain is a diazoketoester in position 3, the intramolecular reaction leads to the expected six-membered ring as a major product of C–H insertion at position 2, but the insertion product at position 3, a spiranic derivative, is also obtained probably due to the stabilization of the intermediate by formation of an additional lactone.[474]



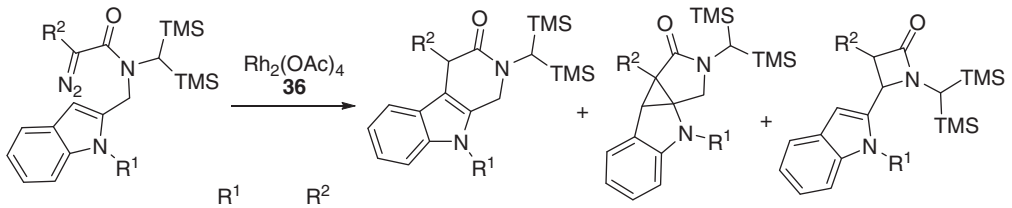
(151)

Pentacyclic structures of indane alkaloids can be obtained by copper-catalyzed intramolecular reaction of a diazocompound prepared from tryptamine (**460**) and isatin (**461**). In this case, the intermediate cyclopropane is stable and it can be characterized. The sequence of reduction of the azide, ring opening of the cyclopropane, and isomerization of the kinetic product to the thermodynamic one leads to the desired structure (**Scheme 107**).[1000]



Scheme 107

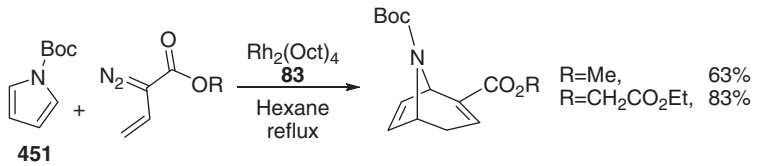
The same pattern, cyclopropanation and rearrangement to C–H insertion product, has been observed in the cyclization of indoles with diazoamide substituents in position 2 catalyzed by Rh carboxylates. The *N*-substitution of the indole and the nature of the carbenoid (acceptor–acceptor or acceptor) control the chemoselectivity with respect to C–H insertions in the side chain and the stability of the intermediate cyclopropane. This methodology opens the way to tetrahydro-*β*-carboline structures, present in indole alkaloids.[467]



R^1	R^2			
Me	CO_2Et	89%	0%	0%
SO_2Ph	CO_2Et	0%	59%	20%
Me	H	0%	95%	0%

(152)

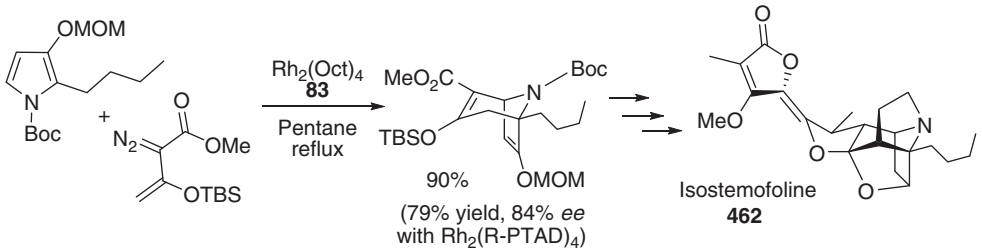
The reaction of vinylketocarbenoids with *N*-Boc-pyrrole **451**, catalyzed by rhodium carboxylates, leads to tropane formation. This is thought to be the consequence of a cyclopropanation/Cope rearrangement tandem process, favored by the presence of a second carbonyl group in the carbenoid (glycolate derivative) and the use of a less electron deficient catalyst that minimizes the formation of products through zwitterionic intermediates.[1001,1002]



451

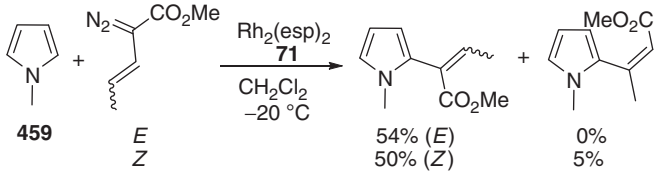
(153)

The asymmetric version of this reaction was first tried with Rh_2(*S*-TBSP)$_4$ **137** with poor enantioselectivity. However, the use of chiral auxiliaries (lactate **286** or pantolactone **287**) allowed, as in the case of furan (**435**), reaching moderate diastereoselectivities.[1003] Some years later, the enantioselectivity was considerably improved up to values of more than 90% *ee* by using Rh_2(*S*-PTAD)$_4$ (**324**) as catalyst.[1004] In fact, this kind of reaction has been used as a starting point for the synthesis of the alkaloid isostemofoline (**462**)[1005] that could be prepared in an enantiopure form using this methodology (**Scheme 108**).

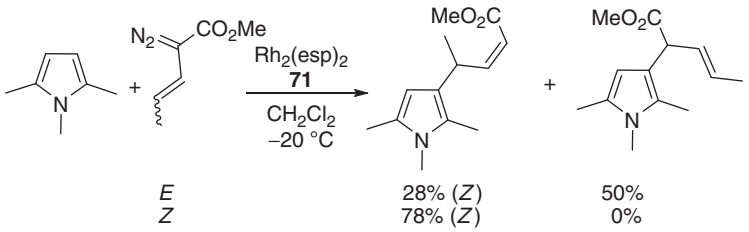


Scheme 108

The high tendency of *N*-alkyl-pyrroles and indoles to undergo C–H insertion reactions has shown some interesting features in the case of 1-propenylcarbenoids. Although the (*E*)-propenylcarbenoid reacts with *N*-methylpyrrole **459** in the presence of $Rh_2(esp)_2$ **71** to give the corresponding product of insertion in position 2, the use of bulkier pyrroles leads to a significant amount of the product of vinylogous reaction. In fact, this is the major product when using the (*Z*)-propenylcarbenoid, and in both cases only the *Z* product is obtained. Reaction can take place in both positions 2 and 3 of pyrrole, depending on the substitution of the starting material. This kind of attack is also observed with indoles.[1006]



(154)



(155)

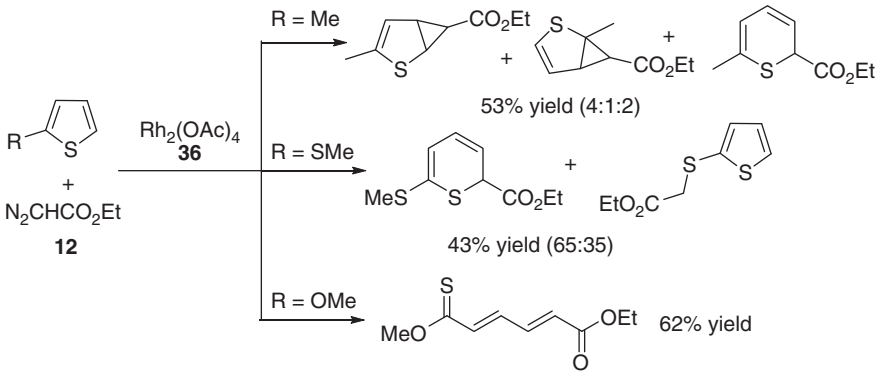
4.20.6.4 Thiophenes

It is well known that the primary reaction of ketocarbenoids with thiophene **463** leads to the formation of a sulfur ylide that can be used as precursor for cyclopropanation of Michael acceptors.[52] In general, thiophene ylides undergo rearrangement to thiophenocyclopropane, the formal product of insertion in position 2, or a dihydrothiopyran due to ring expansion. Substitution in the thiophene may control the chemoselectivity of the process. The reaction of ethyl diazoacetate **12** with substituted thiophenes catalyzed by rhodium acetate **36**, cyclopropanes are the major products in the case of alkyl or silyl substituents, whereas the dihydrothiopyran is obtained with a methylmercapto substituent, and a polyunsaturated acyclic ester-thioester is obtained in the case of alkoxy substituents (Scheme 109).[462]

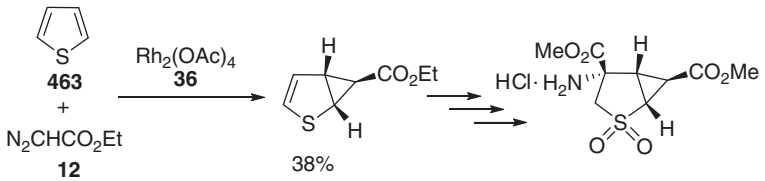
The corresponding cyclopropanation of **463**, obtained in 38% isolated yield with **36**, has been used as a starting material in the synthesis of a precursor of a clinical candidate for the treatment of schizophrenia (Scheme 110).[1007]

In contrast with furans and pyrroles, the reaction of **463** and methylthiophenes with 2-diazocyclohexane-1,3-dione **458** leads to insertion products in position 3 of thiophene. Reaction with 2-methoxy **464** and 2-nitrothiophene **465** affords the insertion in position 5, although in the case of nitro the typical tricyclic structure is obtained but with reverse regioselectivity. With benzothiophene **466**, reactivity was as expected, with 5:1 ratio of regioisomers (Scheme 111).[981]

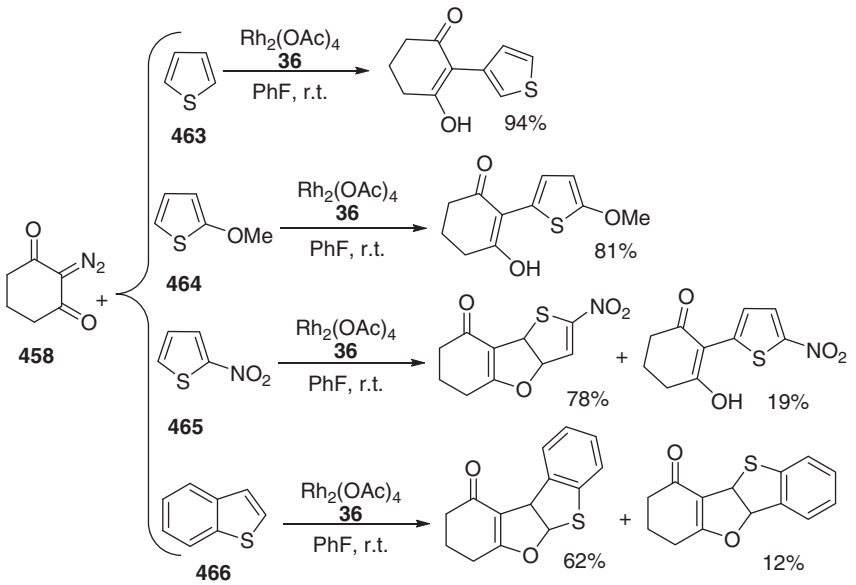
The outcome of intramolecular reactions depends on the starting material. Reaction of 1-diazo-3-(2-thienyl)-2-propanone **467** in the presence of **36** leads to the formal insertion product, 5,6-dihydro-4*H*-cyclopenta[*b*]thiophen-5-one **468**, with 54% yield. However, the 3-substituted thiophene does not produce the expected products of formal insertion in both 2- and 4- positions, but a spiro-disulphide (85% yield) through a [4+2] reversion (analogous to the generation of dienes from furans) followed by a dimerization process.[463]



Scheme 109

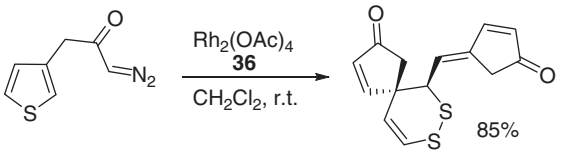


Scheme 110



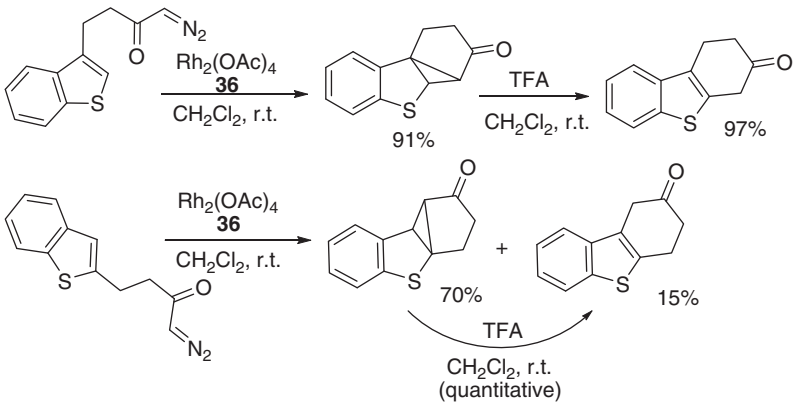
Scheme 111

(156)



(157)

The intermediate cyclopropanes can be detected and even isolated in the case of cyclization of the analogous benzothiophene derivatives, and the final product after treatment with a drop of TFA is always the expected ketone with the aromaticity restored. Only in one case a dimerization product, in the form of disubstituted lactone is obtained (Scheme 112).[464]

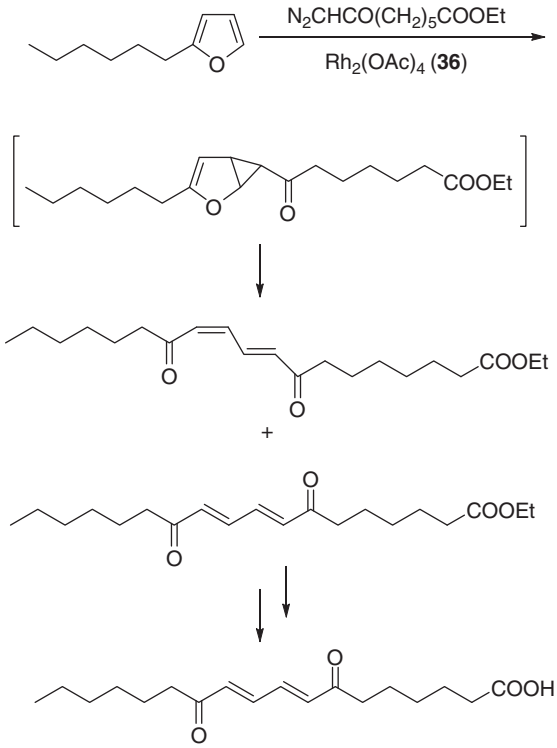


Scheme 112

4.20.6.5 Applications of Cyclopropanation Reactions of Aromatic Compounds to Total Synthesis

4.20.6.5.1 Ostopanic acid

Ostopanic acid **440** is a cytotoxic fatty acid, isolated from the stems and fruits of the *Ostodes paniculata* plant, which inhibits the growth of P-388 lymphocytic leukemia test system *in vivo*. Cyclopropanation reaction is the key step in the total synthesis of ostopanic acid **440** by Sheu et al. Thus, 2-hexylfuran **441** undergoes a cyclopropanation reaction on the less substituted double bond by ethyl 8-diazo-7-oxooctanoate **442** in the presence of $Rh_2(OAc)_4$ **36**, though it was not possible to isolate the cyclopropane (Scheme 113).[982] A mixture of ethyl ostoponate and a regioisomer was obtained in 58% overall yield, though the ethyl ostoponate/regioisomer ratio increased as the reaction was carried out.

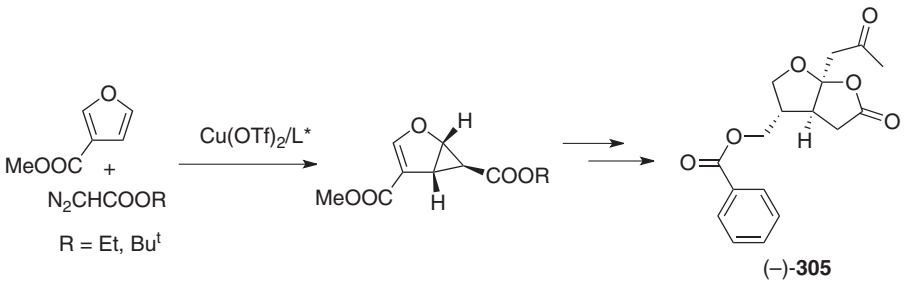


440

Scheme 113

4.20.6.5.2 (−)-Paeonilide

(+)-Paeonilide [(+)-**305**] is a monoterpenoid isolated from the *Paeonia delavayi* plant that exhibits selective inhibition of the platelet aggregation induced by platelet-activating factor, but not by ADP or arachidonic acid. The first step in the enantioselective synthesis of nonnatural (−)-paeonilide [(−)-**305**] by Harrar and Reiser consists of the reaction between methyl 3-furoate with a diazoacetic ester in the presence of a box–Cu catalyst (Scheme 114).[838] The best stereoselectivity results (83% *ee*) were obtained by using **308**, the yield depending on the corresponding diazoacetic ester (*tert*-butyl diazoacetate **133**, 38%; ethyl diazoacetate **12**, 31%) (Table 107).



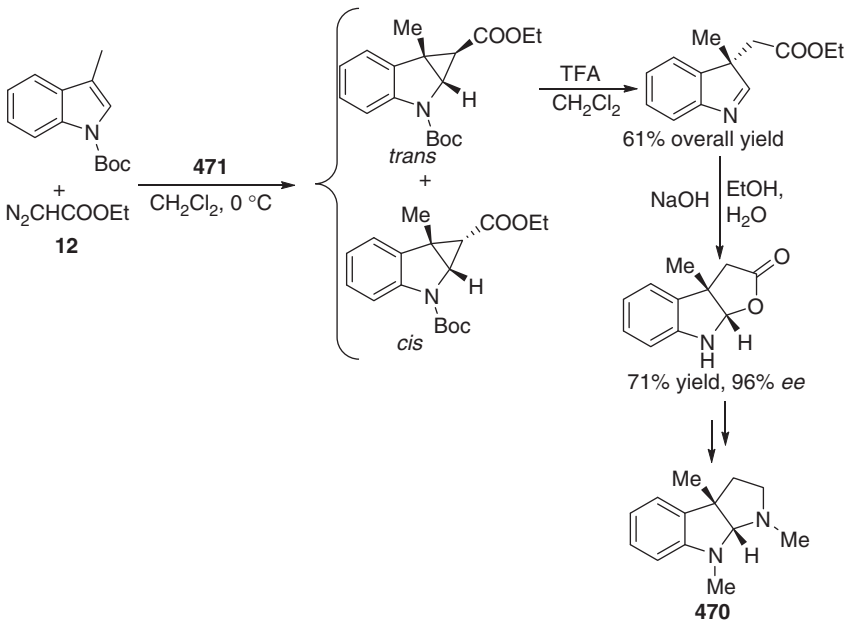
Scheme 114

Table 107 Results of the reaction between methyl 3-furoate and some diazoesters using different ligand-$Cu(OTf)_2$ as catalysts[838]

R	L*	*Yield (%)*	ee *(%)*
Et	**469**	27	74
Bu^t	**469**	38	65
Et	**293**	22	74
Et	**308**	31	83
Bu^t	**308**	38	83
Bu^t	**217**	34	19

4.20.6.5.3 (−)-Desoxyeseroline

The total synthesis of (−)-desoxyeseroline **470** has been carried out by Boysen and coworkers (Scheme 115).[1008] In it, *N*-Boc-protected 3-methylindole has been reacted with **12** in the presence of the gluco–Box catalyst **471** to yield a *trans*/*cis* mixture of

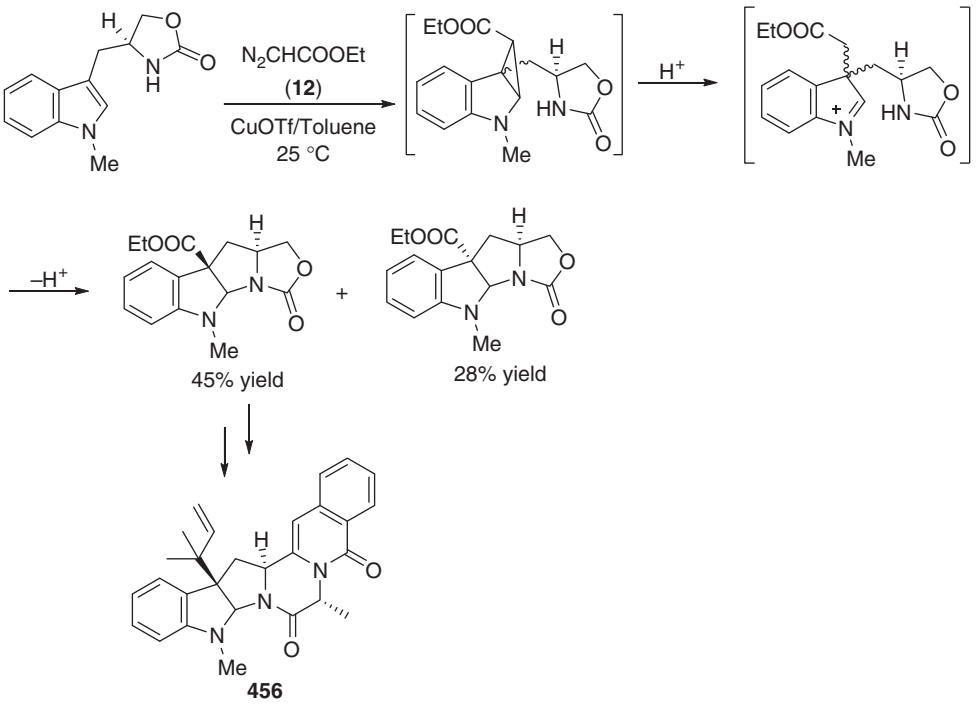


Scheme 115

cyclopropanes. An aliquot of impure *trans*-cyclopropane underwent ring opening by using trifluoroacetic acid to afford a chiral ester (61% overall yield), which was subsequently hydrolyzed to afford a hemiaminal lactone (obtained with 96% *ee*).

4.20.6.5.4 (−)-Ardeemin

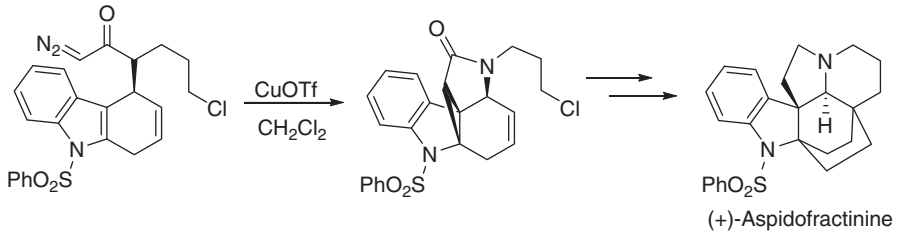
The key step in the total synthesis of (−)-ardeemin **456** by Qin and coworkers consists of a three-step one-pot cascade starting by the catalyzed cyclopropanation reaction between ethyl diazoacetate **12** and a substituted indole (Scheme 116). Excellent results were obtained at milimol scale by using $Cu(OTf)_2$ **472** as a catalyst in CH_2Cl_2 at −35 °C (83% yield, **473**; 5% yield, **474**).[997] However, the change to a multigram scale led to a low yield (22%) as a result of the rapid nonproductive diazoacetate decomposition and a large quantity of black precipitates.[998] Instead, the use of CuOTf **78**-toluene in toluene led to a significant improvement of the results (45% **473** yield and 28% **474** yield at a 50 g scale). The cyclopropanation/ring-opening/iminium cyclization (CRI) strategy through inter- or intramolecular approaches has been demonstrated as a useful technique in the total synthesis of indoline alkaloids.[868]



Scheme 116

4.20.6.5.5 (+)-Aspidofractinine

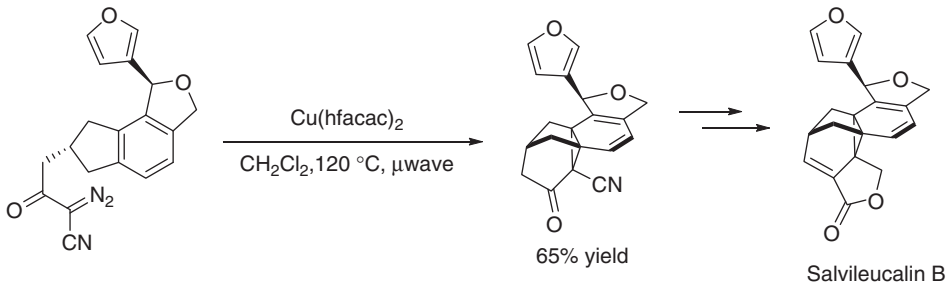
Aspidofractinine **475** is an alkaloid occurring in a number of plants, such as *Aspidosperma refractum*, *Aspidosperma pyrifolium*, *Pleiocarpa tubicana*, and *Kopsia arborea*. The cyclopropanation of an indole derivative was used by Gagnon and Spino in the synthesis of the nonnatural enantiomer of **475**.[1009] Thus, the use of **78** as a catalyst generated the corresponding cyclopropane in 76% yield (Scheme 117).



Scheme 117

4.20.6.5.6 Salvileucalin B

Salvileucalin B **434** is a natural product obtained from *Salvia leucantha*, which exhibits cytotoxicity against A549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cells. An intramolecular cyclopropanation reaction of an α-cyanodiazoketone was carried out in the presence of $Cu(hfacac)_2$ **476** in good yield (65% yield) in the total synthesis of **434** (Scheme 118).[977]



Scheme 118

4.20.7 Conclusion and Perspective

Since the first edition of Comprehensive Organic Synthesis, there has been an increasing interest in the use of metal-carbenoids in organic transformations, as illustrated by the more than 1500 references covering from 1988 to 2013 that the authors have managed for the preparation of this chapter. Some aspects of these transformations have experienced a particular development during these years. The first one is the use of many different metals to stabilize carbene moieties. Apart from rhodium and copper, which are still the undisputed stars (more than half of the work published in this period), many references describe the use of ruthenium, and to a lesser extent, also cobalt, palladium, iron, silver, gold, chromium, osmium, and iridium. The combination of the right metal with the right ligand has represented a dramatic expansion in the synthetic possibilities of ketocarbenoids. It is difficult to think of a substrate that cannot be efficiently cyclopropanated using the adequate system. Probably, the only aspect to improve concerns to chemoselectivity issues in the case of complex substrates, where side reactions, such as C–H insertion, may become problematic.

The second field that has experienced an explosive development has been the use of metal-carbenoids in stereoselective organic reactions. Several hundreds of references deal with enantioselective reactions, compared with the 11 references on enantioselectivity and six on diastereoselectivity cited in the former chapter. It can be said that at present there are excellent tools that allow to obtain cyclopropanes with the desired stereochemistry, in an efficient manner. In this regard, possible improvements can be foreseen in the design and preparation of a catalyst that is able to provide both excellent diastereoselectivities and enantioselectivities with standard reagents, like ethyl diazoacetate. At present, many of the existing catalysts require the use of sterically hindered diazo compounds to obtain improved diastereoselectivity in cyclopropane products.

Finally, there have been important advances in the knowledge of the reaction mechanism involved in these transformations, both from the experimental and theoretical sides. This knowledge should be useful to design more efficient and selective catalytic systems for the addition of ketocarbenes to unsaturated substrates, a research field that is in its maturity, but that enjoys good health and will be still very active for many years for come.

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4.21 Intramolecular 1,3-Dipolar Cycloadditions of Alkenes, Alkynes, and Allenes

RS Menon, CSIR-Indian Institute of Chemical Technology, Hyderabad, India
V Nair, CSIR-NIIST, Trivandrum, India

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4.21.1 Introduction

Half a century has passed since Huisgen's path-breaking work on the conceptual framework, mechanistic rationalization, and demonstration of the generality of 1,3-dipolar cycloaddition reactions appeared in 1963.[1] Huisgen's insightful analysis of a number of well-known but seemingly unrelated examples, amply supported by the experimental evidence generated in the chemist's own laboratory, heralded the emergence of 1,3-dipolar cycloadditions as a new category of reactions. Sustmann's classification of dipolar cycloaddition reactions into three types based on the orbital interactions in 1971 provided additional theoretical footing.[2] Subsequent developments in this area established 1,3-dipolar cycloaddition reactions as arguably the single most important tool for the synthesis of 5-membered heterocycles.[3] The analogous relationship between 1,3-dipolar cycloadditions and Diels–Alder reactions *vis-a-vis* heterocyclic and carbocyclic construction has been recognized, however, the fact that the availability of various classes of dipoles and dipolarophiles allows for a greater degree of versatility remains less appreciated.

Intramolecular dipolar cycloaddition (IDC) is a powerful tool for the synthesis of a variety of fused polycyclic systems. The geometrical constraints imposed by tethering the dipole and dipolarophile, generally lead to very high levels of regio- and stereoselectivities. These preferences may often differ from that observed for the corresponding intermolecular reactions which are controlled mainly by electronic factors. Additionally, IDC reactions differ from the intermolecular variants in their capacity to create carbocyclic rings of varying sizes. Therefore, it is not surprising that IDC reactions have featured as key bond-forming events in a large number of synthetic endeavors targeted at natural products.[4]

A handful of reviews are available that cover the literature of IDC reactions.[4,5] In the Sections 4.21.2–4.21.9, discussions on IDC reactions of various dipoles, mainly focusing on reports published after 1991, are presented. A large body of work is available in the case of each of the dipoles and a gentle emphasis has been laid on IDC reactions employed in targeted syntheses to limit the chapter to an acceptable length.

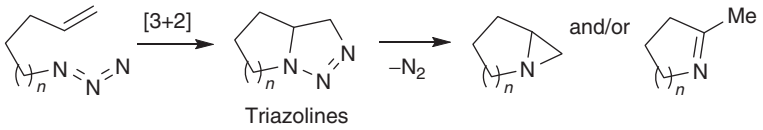
4.21.2 Azides

Azides constitute one of the most studied classes of 1,3-dipoles due to the stability of organic azides when compared to other common dipoles.[6] Additionally, the azide group can be easily incorporated into organic compounds by nucleophilic displacement reactions.[7] The dipolar cycloaddition of an azide to an alkene produces a triazoline, whereas cycloaddition to an alkyne affords the aromatic triazole. The azide–alkene cycloadducts often serve as precursors for aziridines or imines which are generated via thermal extrusion of nitrogen from triazolines at elevated temperatures. Thermal cycloaddition of azides with alkynes was initially described by Huisgen[8] in the 1960s and this reaction is commonly referred to as the Huisgen cycloaddition (in view of the scientist'spioneering contributions to the area, it is more appropriate that the term 'Huisgen cycloaddition' encompasses all

1,3-dipolar cycloadditions rather than just the azide–alkyne cycloaddition alone). The discovery of copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC) leading to the selective formation of 1,4-substituted regioisomers of triazoles, independently by Sharpless and Meldal marked the advent of 'click chemistry' in 2001.[9] Since then, this general, regioselective and mild method for 1,2,3-triazole synthesis has gained immense popularity. In addition to being the most common method for triazole synthesis, the CuAAC reaction assumes importance due to its bioorthogonality[10] and its ability to deliver macrocycles.[11] Recently, ruthenium (II)-catalyzed azide–alkyne cycloadditions (RuAAC) have been shown to selectively produce the 1,5-substituted regioisomers of 1,2,3-triazoles.[12]

4.21.2.1 Intramolecular Azide–Alkene Cycloaddition (IAC) Reactions

Most of the IAC reactions are thermally promoted and require no catalysts/mediators. Although the triazoline cycloadducts resulting from the IAC reactions constitute an interesting class of heterocycles, they are seldom isolated. The synthetic applications of IAC reactions generally pivot around the thermal decomposition of the cycloadducts to afford corresponding imines or aziridines or mixtures of both (Scheme 1).



Scheme 1

Formation of imines via the IAC reaction has been employed for targeted syntheses of natural products, especially alkaloids. (−)-Slaframine **1** (indolizidine family),[13] (+)-crotanecine **2** (pyrrolizidine family),[14] crinane **3** (ethanophenanthridine family),[15] and tylophorine **4** (phenanthroindolizidine family)[16] are just a few alkaloids that are accessible by this method (Scheme 2).

Thermal extrusion of nitrogen from triazolines often produces a mixture of the aziridine and imine products. The mixture can, however, be reduced to a single secondary amine product under conditions of catalytic hydrogenation. This method has been applied in the total syntheses of the phenanthroindolizidine and phenanthroquinolizidine alkaloids, antofine, and cryptopleurine. Interestingly, both *cis* and *trans* isomers of the azido-olefin **5** underwent cycloaddition–nitrogen extrusion cascade to generate imine **6** and aziridine **7** in roughly the same ratio (approximately 2:1). The mixture on reduction afforded the pyrrolidine **8** which was converted into the natural product via the Pictet–Spengler reaction (Scheme 3).[17]

Synthetic potential of aziridines is well documented[18] and it is not surprising that nitrogen extrusion from IAC adducts to form aziridines has also found numerous successful applications in the synthesis of natural and nonnatural products alike. For example, an intramolecular azide–enone dipolar cycloaddition reaction was the cornerstone in the synthesis of an azaspirocyclic ketoaziridine **9**, which is structurally related to the antitumor alkaloid, cephalotaxine **10** (Scheme 4).[19]

An azide–allylsilane 1,3-dipolar cycloaddition was used in the synthesis of a benzazoc-3-ene derivative **11**, which has been recognized as a valuable precursor for the synthesis of the antitumor agents, mitomycin C and FR-900482. A completely diastereoselective dipolar cycloaddition between the azide and allylsilane moieties afforded a triazoline which on photolysis furnished the aziridine **12**. A TBAF (or other bases)-promoted homo-Brook rearrangement of **12** furnished the target benzazocene **11**.[20] Similarly, the azide **13** underwent an IAC reaction to yield the triazoline **14** as a mixture of *anti* and *syn* (7:1) isomers. Photochemical extrusion of nitrogen and subsequent hydrolysis furnished benzazocene **15** (Scheme 5).[21]

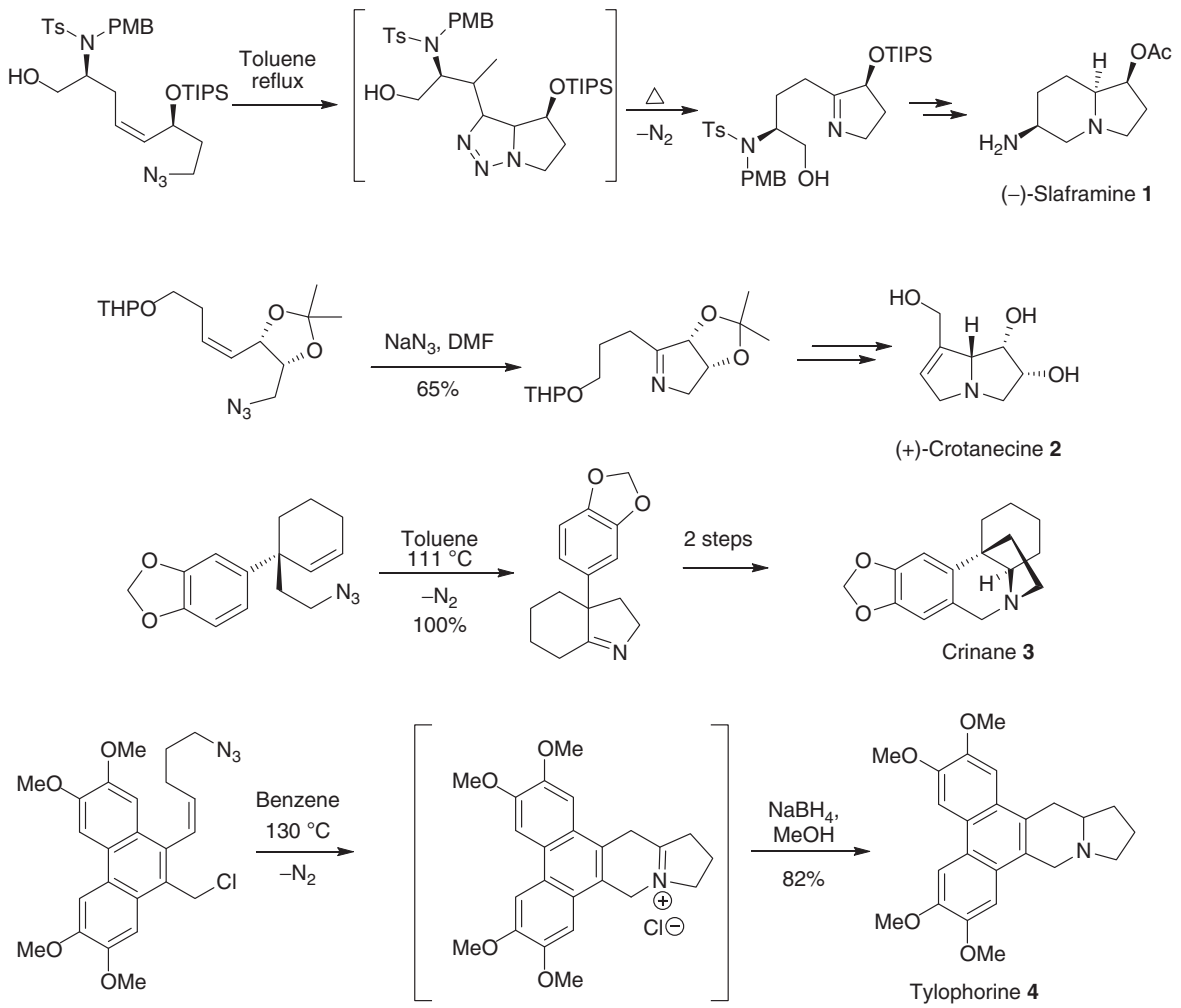
The enantioselective synthesis of the water-soluble B-vitamin, (+)-biotin employed an IAC reaction as the key step. The 10-membered azido-thiolactone **16**, prepared in a few steps from L-(+)-cysteine, on thermolysis in water afforded a mixture of isomers **17** and **18**. The extrusion of nitrogen from cycloadduct **19** is assisted by the proximal nucleophilic sulfur atom. The resultant tricyclic sulfonium intermediate **20** on hydrolytic opening generates the carboxylic acid side chain of biotin (Scheme 6).[22]

IAC reaction has also found use in the synthesis of the tricyclic ring system present in the aspidosperma alkaloid, vindoline. Thermal cycloaddition of the azido-olefin **21** and subsequent nitrogen loss afforded the aziridine **22** as a single isomer. The latter was carried forward to construct the tricyclic system **23** of vindoline in a few steps (Scheme 7).[23]

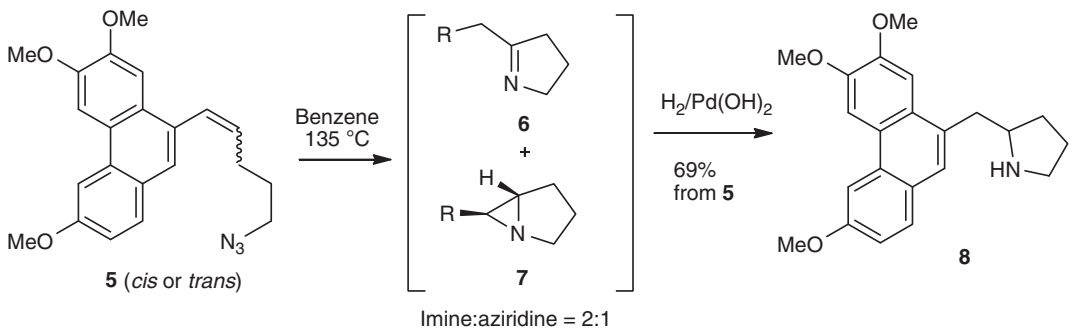
Analogs of deoxynojirimycin, a natural glucosidase inhibitor, were synthesized from sugar-derived azido–alkene **24** via a one-pot operation involving a stereoselective IAC reaction, nitrogen extrusion, and nucleophilic opening of the resultant aziridine **25** (Scheme 8).[24] A similar sequence of reactions performed on L-sorbose-derived alkene **26** afforded the polyfunctional bicyclic product **27** (Scheme 9).[25]

Isoindoles **28** were formed on heating α-azido carbonyl compounds bearing a 2-alkenylaryl moiety in the *ortho*-position (Scheme 10). The presence of a carbonyl moiety at the α-position of the azide unit was found to be indispensable for the isoindole formation.[26]

Azides attached to the enediyne units exhibited interesting reactivity patterns in their intramolecular cycloaddition reactions. The aromatic enediyne azide **29** underwent cycloaddition with the terminal alkene to afford the traizoline fused, stable enediyne **30**. The nonaromatic enediyne **31**, however, furnished the benzotriazine product **32** in 35% isolated yield under similar conditions. This transformation is presumably initiated by the dipolar cycloaddition to form the triazole–aziridine **33**. It suffers ring opening to form the cyclic allene **34** which undergoes a Myers–Saito cyclization to generate the diradical **35**. Subsequent hydrogen



Scheme 2

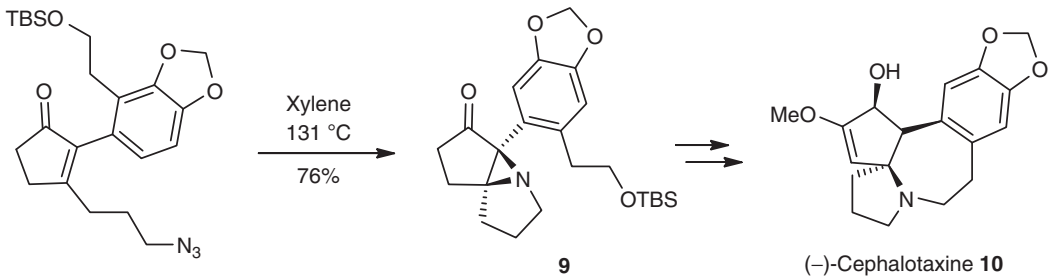


Scheme 3

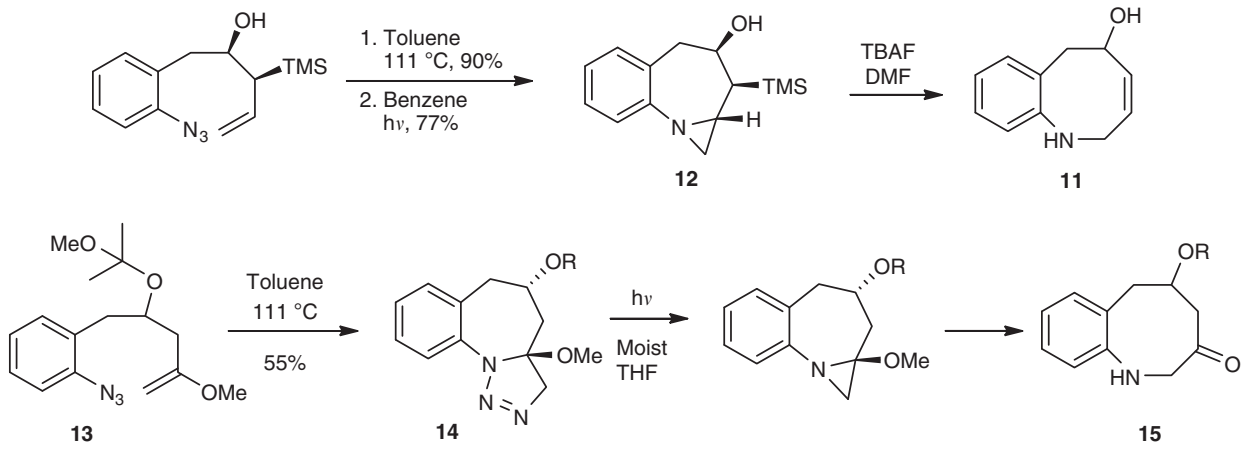
atom abstraction from 1,4-cyclohexadiene results in the formation of the triazine **36** which tautomerizes to the final product **32** (Scheme 11).[27] Supercoiled plasmid deoxyribose nucleic acid suffered single-strand cuts when incubated with the enediyne **31**, in accordance with the involvement of the diradical **35**.

4.21.2.2 Intramolecular Azide–Alkyne Cycloaddition Reactions

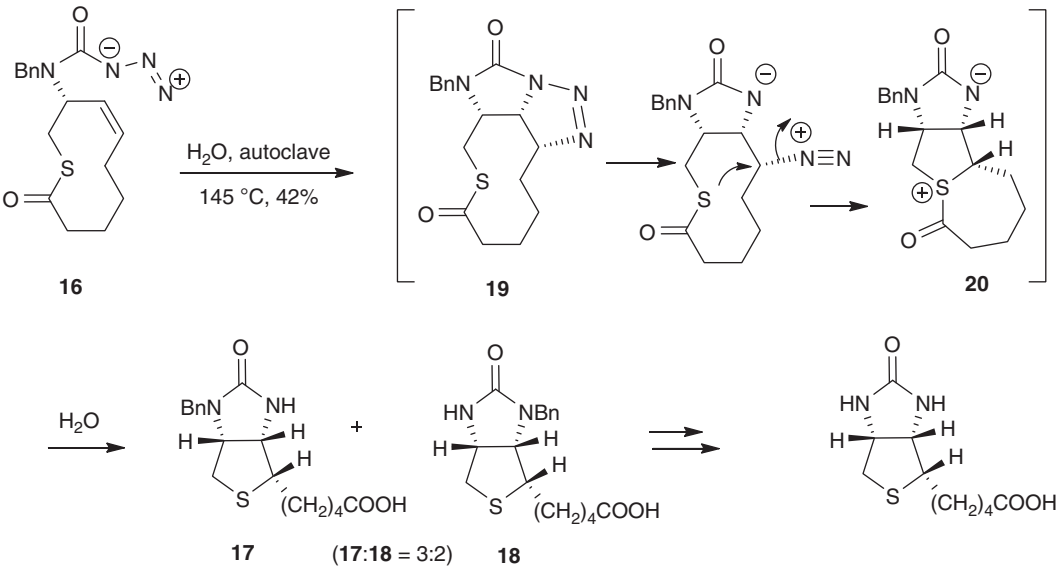
The first example of an intramolecular azide–alkyne cycloaddition was reported in 1975.[28] Intramolecular cycloadditions proceed efficiently under thermal mediation only when the size of the newly formed ring is kinetically favored and the steric factors are not



Scheme 4



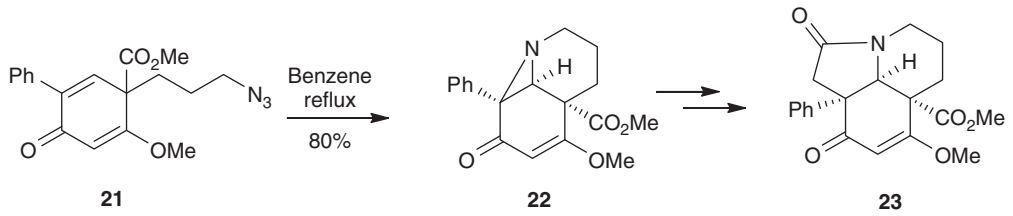
Scheme 5



Scheme 6

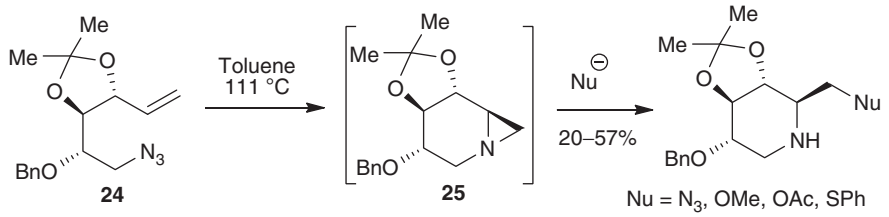
prohibitive. However, ever since the emergence of CuAAC reaction as the 'cream of the crop' in click chemistry at the dawn of the century, azide–alkyne cycloaddition reactions have found widespread applications in natural product synthesis, medicinal chemistry, and materials science.[29]

Unnatural 7-aza analogs of anticancer bisbenzocyclooctadiene lignan lactones (−)-steganacine and (−)-steganone were synthesized via a microwave-assisted intramolecular azide–alkyne cycloaddition of biaryl-azidoalkynes **37a**,**b**. The cycloadduct



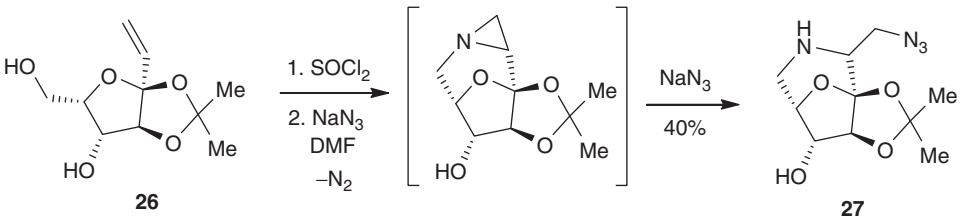
21 22 23

Scheme 7



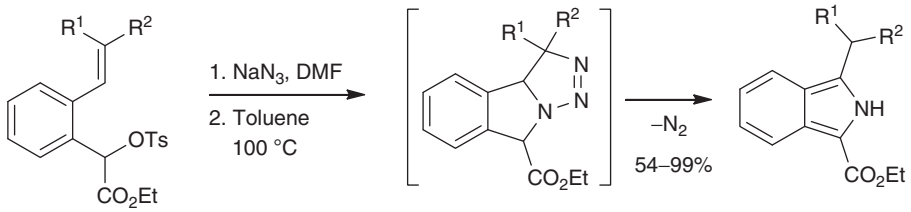
24 25

Scheme 8



26 27

Scheme 9



28

R^1, R^2 = H, Me, Ph, 4-OMe-C_6H_4, 1-hexenyl, cyclopropyl, cyclobutyl, cyclohexyl

Scheme 10

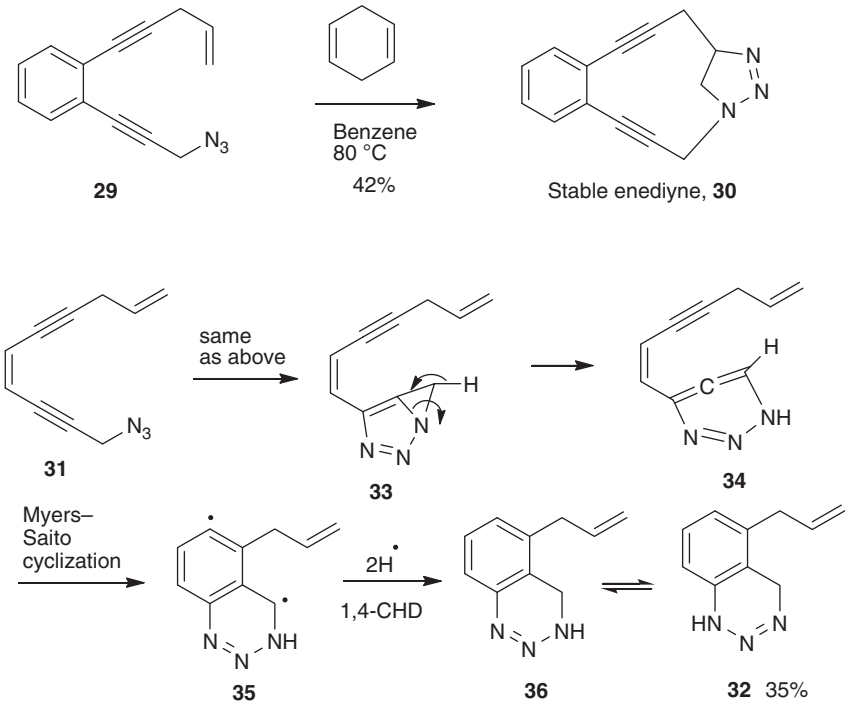
dibenzotriazolo[1,5]azocine **38** also exhibited an interesting biological profile. The cycloadditions did not occur on conventional heating. The acetate derivative **37b** being less rigid than the ketone **37a** required lower activation energy for the cycloaddition process and thereby afforded a higher yield of the product (Scheme 12).[30]

1-(2-Haloaryl)propionamides **39** on treatment with sodium azide in the presence of copper iodide underwent an azide–alkyne cycloaddition followed by an intramolecular Ullmann-type coupling reaction to afford [1,2,3]triazolo[1,5-a]quinoxalin-4(5H)-ones **40** (Scheme 13).[31]

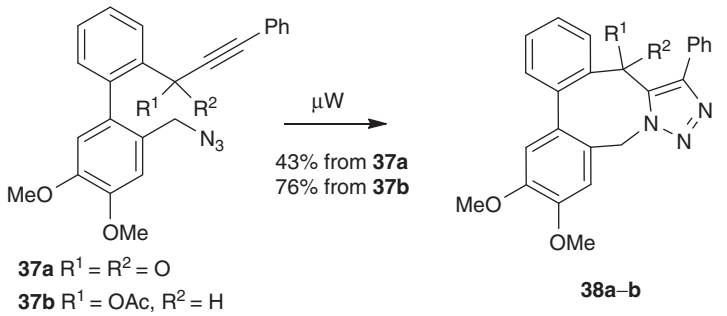
Intramolecular Cu(I)-catalyzed cycloaddition of azidoalkynes **41** derived from salicylaldehyde furnished triazolobenzoxazepine derivatives **42** that exhibit antibacterial as well as antifungal properties (Scheme 14).[32]

Enantiopure phenylglycidol derivatives **43** endowed with alkynyl appendages on treatment with sodium azide underwent stereospecific and regioselective epoxide ring opening followed by intramolecular azide–alkyne cycloaddition under copper-free conditions. A number of triazolooxazepinols, triazolodiazepinols, and triazolothiazepinols were accessed by this method (Scheme 15).[33]

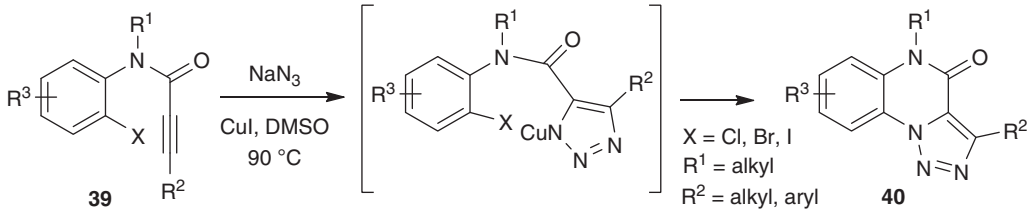
A variety of phenyl azides underwent facile thermal intramolecular azide–alkyne cycloaddition reactions to afford annulated tetracyclic benzazepine derivatives **44**. The substrate assembly and the ensuing cycloaddition were carried out in a one-pot



Scheme 11



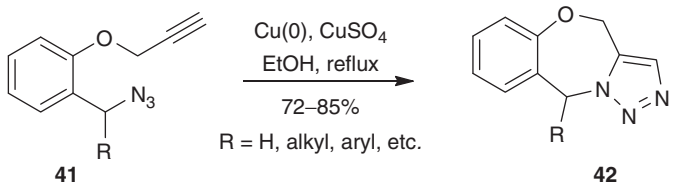
Scheme 12



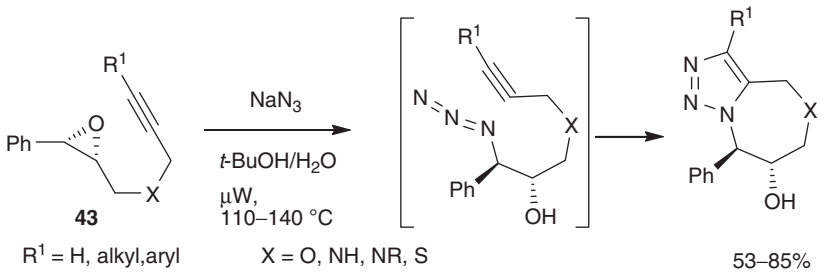
Scheme 13

operation wherein 2-alkynyl indoles **45** were treated with *o*-azido-*β*-nitrostyrenes **46** in the presence of ytterbium triflate. A carbon–carbon bond between the C-3 position indole unit and the nitrostyrene moiety is installed by a Lewis acid-catalyzed Michael addition which is followed by an IDC reaction between the azide and thependant alkyne. It was observed that the isolated Michael product **47** underwent facile dipolar cycloaddition even in the absence of $Yb(OTf)_3$ (Scheme 16).[34]

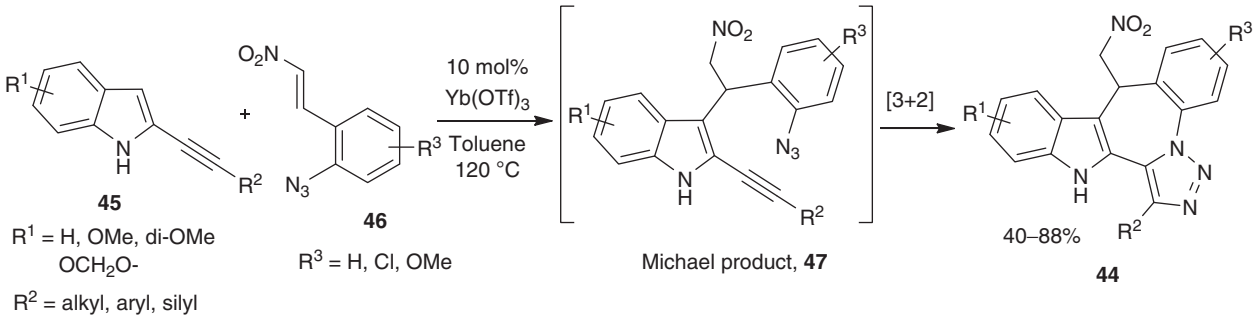
2-Azidobenzaldehydes **48** served as the starting materials for the synthesis of a variety of 1,2,3-triazole-fused 1,4-benzodiazepines **49–50** in intramolecular azide–alkyne cycloaddition reactions. The cycloadducts were employed in a diversity oriented synthesis (DOS) approach to generate a variety of analogs incorporating the parent heterocyclic scaffold (Scheme 17).[35]



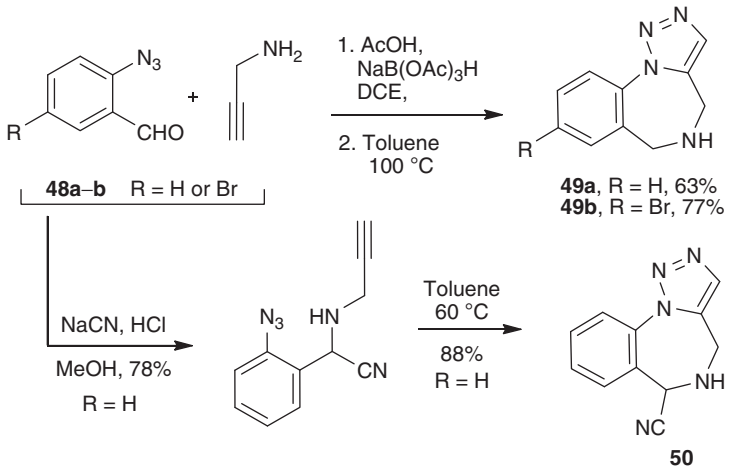
Scheme 14



Scheme 15



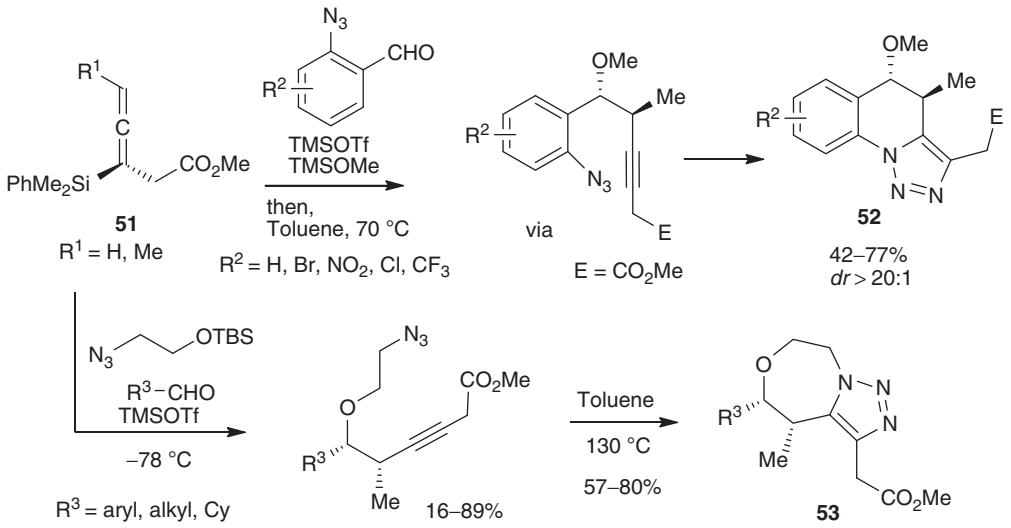
Scheme 16



Scheme 17

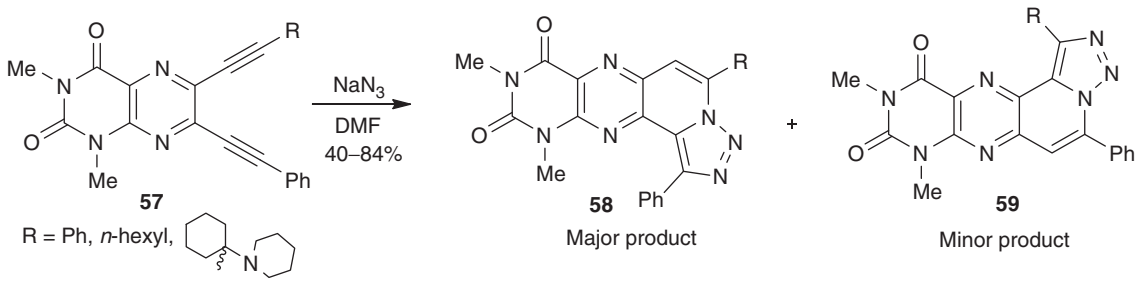
A one-pot three-component reaction of enantioenriched allenylsilanes **51**, aldehydes and silyl ethers leading to the formation of various 1,2,3-triazole-fused ring systems **52**–**53** was reported in 2010. The alkyne unit which takes part in the dipolar cycloaddition is unraveled on the addition of allenylsilane to the aldehyde. The azide unit is introduced either as an aldehyde substituent or as a silyl ether appendage. Representative examples are depicted in Scheme 18. The ability to modify all the three

components and the stereochemical control make this tandem propargylation–dipolar cycloaddition sequence a powerful synthetic tool.[36]

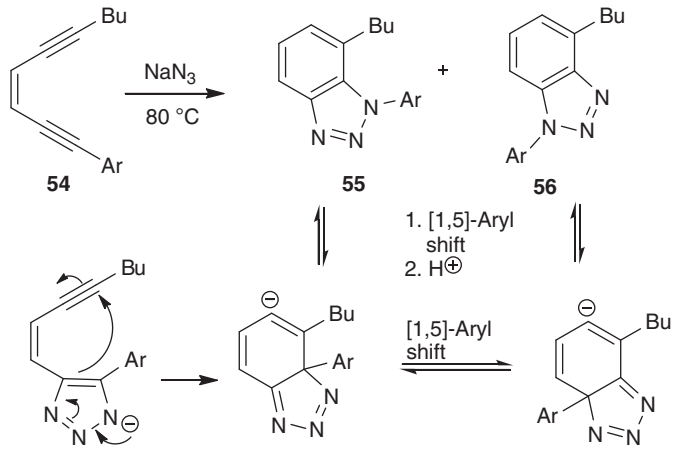


Scheme 18

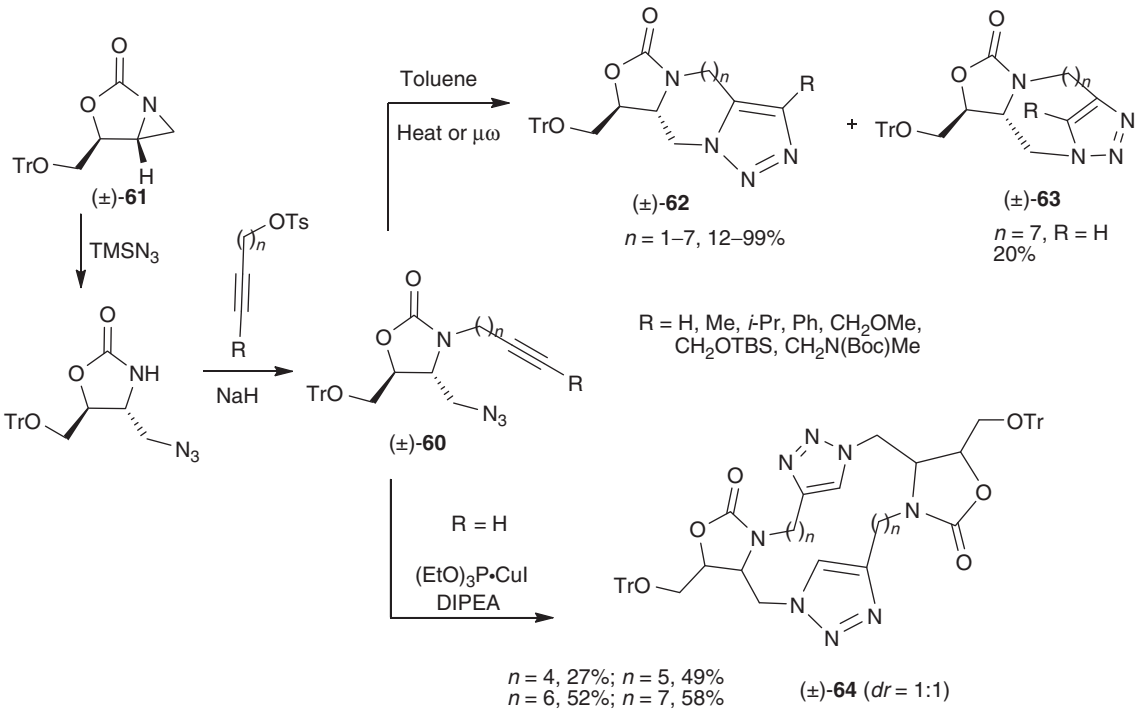
Cascade cyclization of enediynes **54** initiated by azide anion addition furnished 1-aryl-1H-benzotriazoles **55–56**. However, 6,7-dialkynyl-1,3-dimethyllumazines **57**, under similar conditions afforded triazole derivatives **58–59** (Scheme 19).[37] The annulation proceeds presumably via dipolar cycloaddition of azide anion to the less electron rich of the alkynes followed by heterocyclization of the resultant triazole *N*-anion to the adjacent alkyne unit.



Scheme 19



Triazole-fused heterocycles of varying ring sizes were constructed via intramolecular azide–alkyne cycloaddition of the oxazolidin-2-one derivatives **60**, which in turn were synthesized from the fused ring aziridine **61**. Thermally promoted cycloadditions proceeded smoothly in refluxing toluene to afford 6- and 7-membered fused triazoles **62** ($n=1, 2$) (Scheme 20).[38] However, when the tether length exceeded two carbons, microwave irradiation was required to ensure satisfactory rates for the annulations. A 1,4-triazole **63** was formed as a minor product along with the expected 12-membered 1,5-triazole **62** ($n=7$) when the tether length was long enough to overcome the constraints of a bridgehead double bond. Dimeric cycloadducts **64** were obtained in moderate yields when an iodo(triethyl phosphite)copper(I)-/*N*,*N*-diisopropylethylamine (DIPEA) catalyst system was employed along with microwave irradiation; however, sodium ascorbate–$CuSO_4$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)–CuI combinations failed to produce any dimeric products. The products **62–63** were designed as conformationally restrained analogs of ribonucleic acid-binding oxazolidinones.



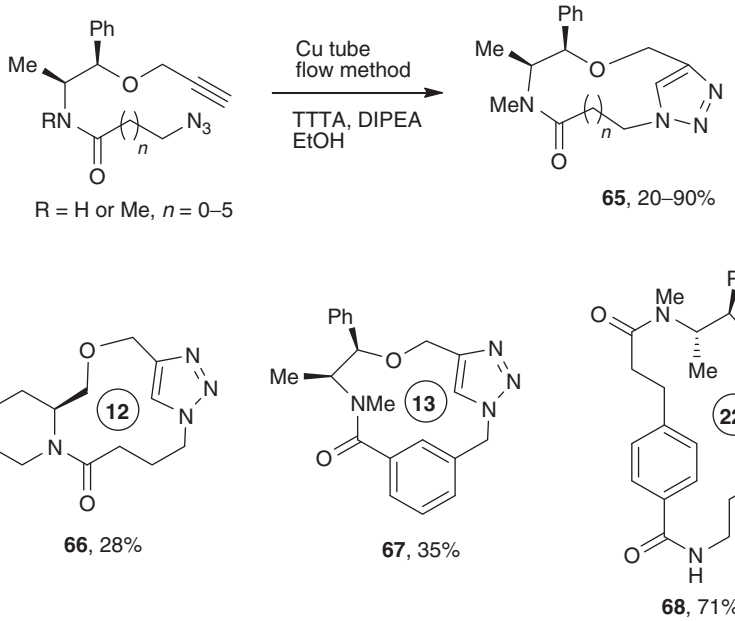
Scheme 20

A variety of triazole-containing macrocycles **65–68** of varying size and functionality were synthesized by CuACC reaction conducted in a flow system with copper tubing as a reaction vessel at high temperatures. Macrocyclic drug-like compounds with ring sizes ranging from 12 to 22 could be accessed in a few minutes in the presence of copper-chelating ligand tris[(1-*tert*-butyl-1*H*-1,2,3-triazolyl)methyl]amine (TTTA) and diisopropylamine (Scheme 21).[39] The annulation occurs at the surface of the copper tube where a favorable 'pseudodilution' scenario arises in which a surface-bound cyclization precursor is held at a sufficient distance from other molecules and intermolecular interactions are, therefore, minimized.

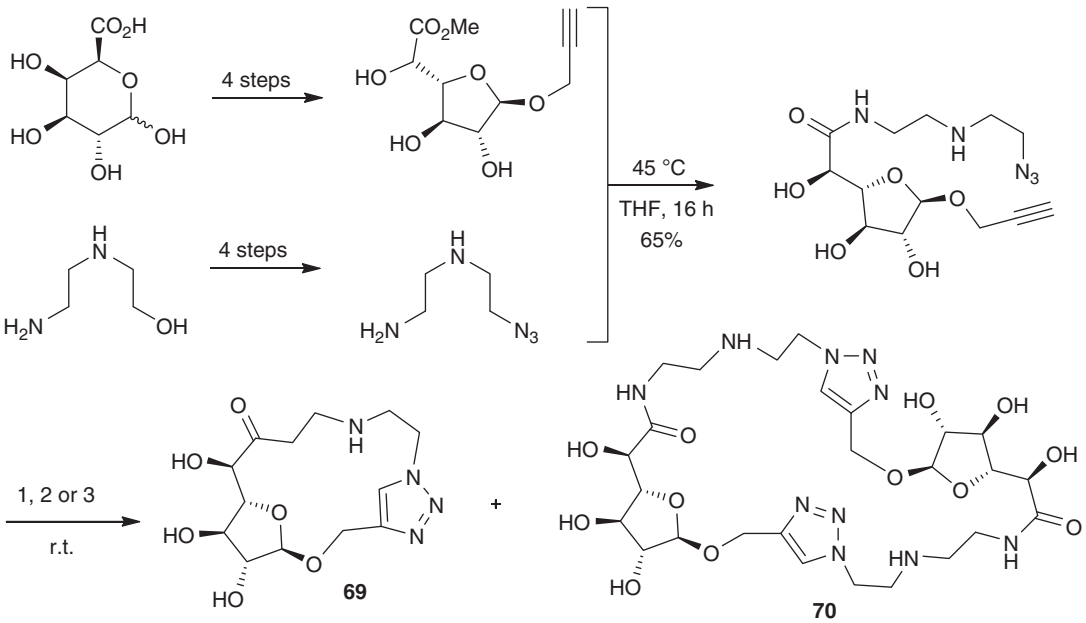
A galacturonide-based macrocycle **69** that incorporates an amide linkage and a triazole ring was synthesized by means of an intramolecular azide–alkyne cycloaddition reaction. The 16-membered macrocycle **69** was obtained along with a symmetric dimer **70** in different ratios depending on the conditions (Scheme 22). This methodology has also been employed for the synthesis of 12- to 31-membered 5-iodo-1,2,3-triazole-contacting macrocycles from the corresponding 1-iodoalkynes.[40]

The exceptional propensity of CuAAC reaction to allow the formation of macrocyclic systems was demonstrated by the click-annulation reactions of α-azide-ω-alkyne-functionalized oligo(ethylene glycol) derivatives **71**. The cyclization substrates were assembled using iterative click chemistry and protection–deprotection sequences. Macrocycles with ring sizes ranging from 14 to 56, having 1–8 triazole units incorporated within them, could be fabricated under 'pseudo-high-dilution' conditions in excellent yields (Scheme 23).[41] The product macrocycles **72** are crown ether-based analogs possessing electron-rich aromatic triazole units capable of supramolecular interactions. Click chemistry has also been employed for the synthesis of aryl amide-based macrocycles.[42]

CuAAC reaction has been employed as a macrocyclization tool in the synthesis of a library of jaspaklinolide analogs **73** where the *E*-double bond is replaced by a 1,2,3-triazole moiety. It was observed that this method of macrocyclization was superior to the more conventional methods such as macrolactonization and lactamization (Scheme 24).[43]



Scheme 21

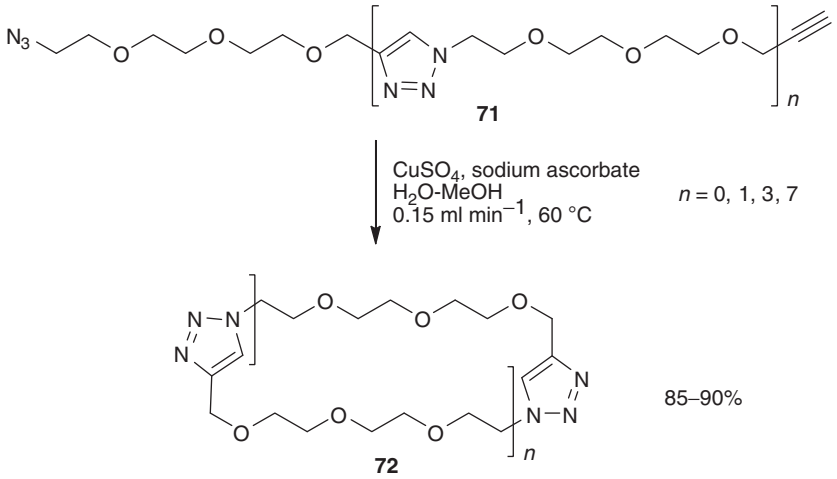


1. $CuSO_4$, sodium ascorbate, H_2O; 84% yield, **69**:**70** = 4:1
2. CuI, THF/CH_3CN, DIEA; 90% yield, **69**:**70** = 7:3
3. CuI, H_2O, DIEA; 54% yield, only **70** formed

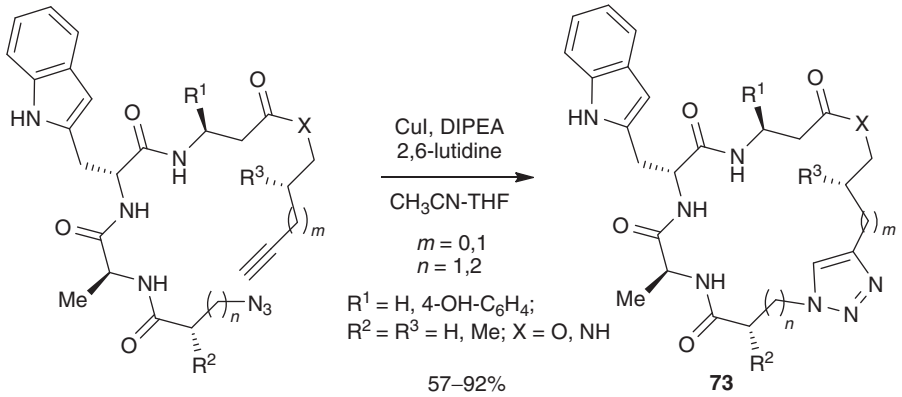
Scheme 22

The first example of a ruthenium-catalyzed intramolecular azide–alkyne cycloaddition was reported in 2009. This regioselective reaction afforded macrocyclic 1,5-disubstituted triazoles **74** from a variety of azido-alkyne substrates (e.g., **75**). Notably, CuAAC reaction on the same substrate afforded the 1,4-regioisomeric triazole **76** within a one carbon larger macrocycle (Scheme 25).[44]

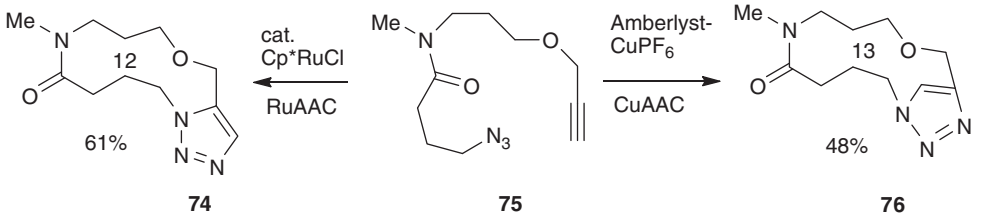
CuAAC reaction has been successfully employed for the intramolecular side-chain to side-chain cyclization of peptides. This is an established approach to achieve stabilization of specific conformations and a recognized strategy to improve resistance toward proteolytic degradation as the triazole products resemble amides in electronic and steric aspects, at the same time being resistant toward hydrolysis.[45]



Scheme 23



Scheme 24

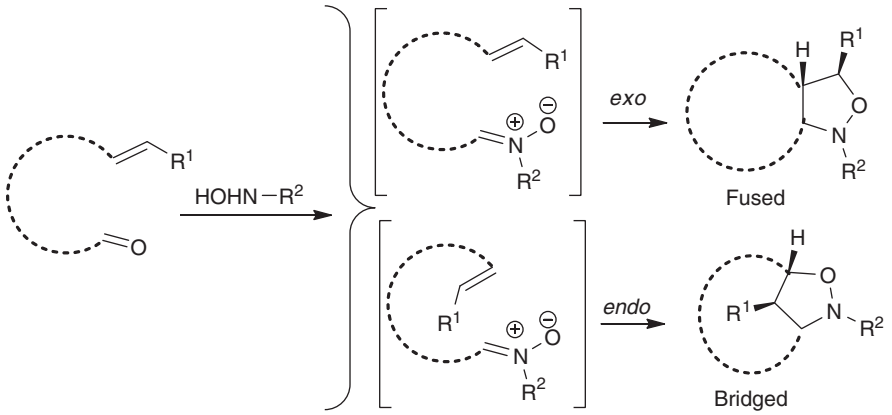


Scheme 25

4.21.3 Nitrones

Nitrones are usually generated by the condensation of an aldehyde and an *N*-substituted hydroxylamine[46] or the oxidation of a hydroxylamine.[47] Some nitrones are stable enough to permit isolation and even chromatography. The nitrone–alkene dipolar cycloaddition is often reversible. Therefore, nitrones may be temporarily masked as their cycloadducts with styrene or methyl acrylate and later regenerated via thermal cycloreversion. An intramolecular nitrone–alkene cycloaddition (INAC) reaction to afford fused isoxazolidines was first reported by LeBel in 1959.[46] Since then, it has become a widely used method for the construction of medium-sized carbocyclic and heterocyclic rings.[5b,48] INAC reactions are kinetically controlled and in the case of substituted alkenes the configuration of the latter is preserved. Two modes of annulation are possible, namely, *exo* or *endo*, leading

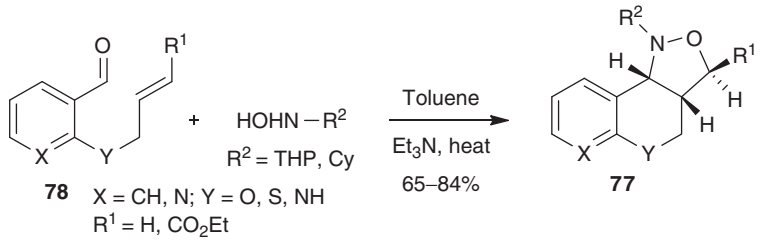
to fused or bridged bicyclo systems, respectively (Scheme 26). Reductive cleavage of the N–O bond of cycloadducts with Pd or Raney Nickel leads to γ-amino alcohols. Chiral nitrones derived from amino acids or sugars, have found widespread use in asymmetric variants of INAC reactions.[49]



Scheme 26

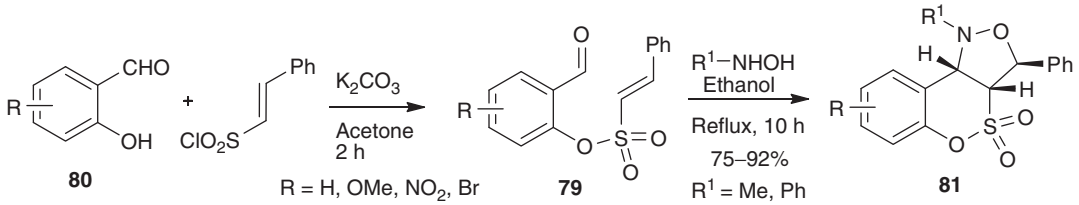
4.21.3.1 INAC Reactions

Applications of INAC reactions in targeted synthesis usually exploit the facile reductive opening of the isoxazolidine cycloadducts to afford 1,3-aminoalcohols. A number of studies, however, have focused on the design and synthesis of various isoxazolidine cycloadducts as the final targets. For example, structural analogs **77** of the fused pyrrolloquinoline tricyclic system found in the alkaloid martinelline were synthesized by INAC of substrates **78**. The tricyclic isoxazolidine products included tetrahydrothiochromenoisoxazoles, hexahydroisoxazolequinolines, and tetrahydroisoxazolepyranopyridines. The cycloaddition could be accelerated by microwave heating in one case. A pyridine-derived dipole afforded the cycloadduct only when the alkene was substituted with an electron-withdrawing group (Scheme 27).[50]



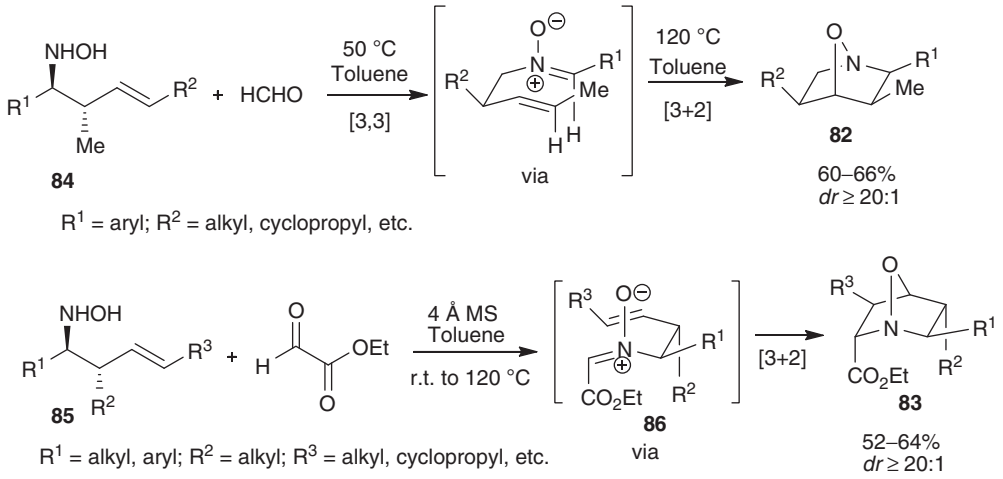
Scheme 27

2-Formylphenyl-(*E*)-2-phenylethenesulfonates **79** derived from substituted 2-hydroxybenzadehydes **80** underwent facile INAC reactions on treatment with *N*-methyl and *N*-phenyl hydroxylamines in boiling ethanol to afford various isoxazolidine-annulated δ,γ-benzo-δ-sultones **81** in high yields. The exclusive formation of single diastereomers indicates that *Z*-nitrones are involved in the cycloaddition (Scheme 28).[51]



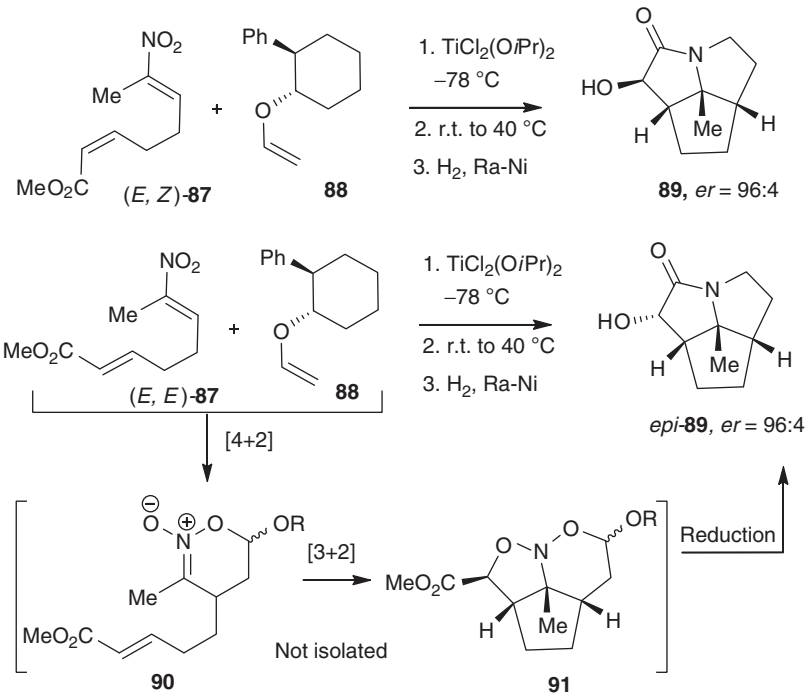
Scheme 28

Densely functionalized 1-aza-7-oxabicylo[2.2.1]heptanes **82–83** were synthesized from stereodefined primary homoallylic hydroxylamines **84–85**. Two distinct heterocyclic skeletons could be accessed from similar substrates via divergent pathways which involved either a direct intramolecular nitrone–alkene dipolar cycloaddition or a sequential [3,3]-sigmatropic rearrangement followed by an INAC reaction. The homoallylic hydroxylamines **84** on heating with formaldehyde (or acetaldehyde) in toluene initially at 50 °C and then at 120 °C underwent nitrone formation, [3,3]-sigmatropic rearrangement, and subsequent intramolecular [3+2] cycloaddition to generate the bicyclic products **82**. Nitrones **86** generated from ethyl glyoxylate, however, participated in the [3+2] cycloaddition directly and afforded the products **83**. Both the reactions proceed with excellent diastereoselectivity. Additionally, asymmetric variant of the methodology was also developed by employing optically pure homoallylic hydroxylamines as starting materials (Scheme 29).[52]



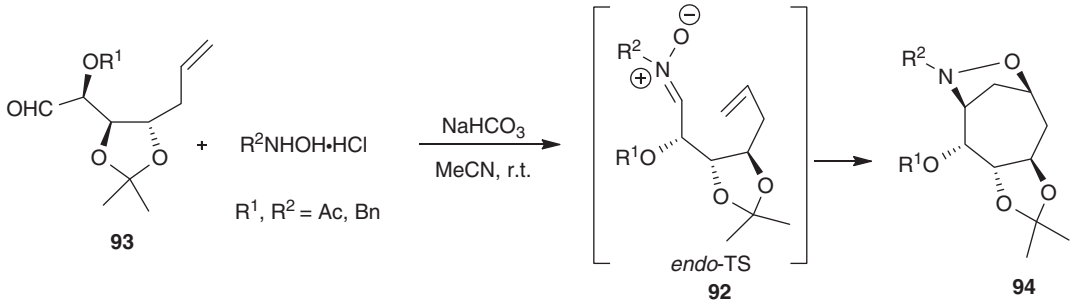
Scheme 29

A tandem [4+2]/[3+2] cycloaddition of nitroalkene **87** with chiral vinyl ethers **88** afforded the polycyclic hydroxyl lactams **89** and *epi*-**89** which were further elaborated to afford a series of novel chiral phase transfer catalysts. The hetero-Diels–Alder reaction of nitroalkene **87** with the vinyl ether mediated by $TiCl_2(Oi\text{-}Pr)_2$ is followed by an IDC of the resultant nitronate **90** with the pendant alkene. The nitrosoacetal **91** thus formed on hydrogenolysis generated the final products, viz., the tricyclic lactams **89** (Scheme 30).[53]



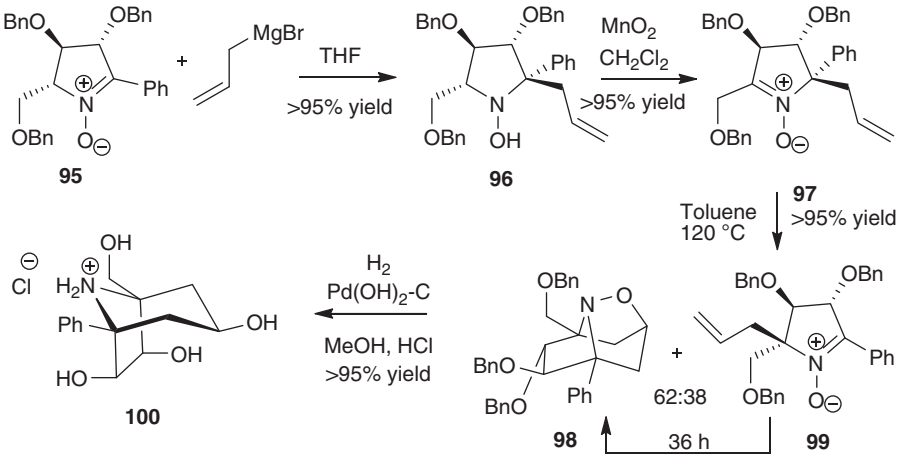
Scheme 30

INAC reactions of nitrones **92** derived from hept-6-enoses **93** carrying a *trans*-acetonide group in the chain exclusively afforded the bridged isoxazolidine cycloadducts **94**. Computational models suggested that the transition state leading to the bridged bicyclo [4.2.1]isoxazolidine (*endo* product) is more stabilized than the one leading to the fused *exo* cycloadduct (Scheme 31).[54]



Scheme 31

Chiral nitrone **95** derived from D-arabinose underwent stereoselective addition to allylmagnesium bromide to afford the hydroxylamine **96** which on oxidation with MnO_2 generated the substituted nitrone **97** in quantitative yield (Scheme 32). It readily took part in a stereoselective IDC to afford the expected cycloadduct **98** along with the rearranged nitrone **99**. The latter is presumably formed via a 2-aza-Cope rearrangement of **97** and on prolonged heating **99** also affords the same cycloadduct **98**. Catalytic hydrogenolysis of **98** leads to the formation of the novel norptropane analog **100** in quantitative yield.[55]



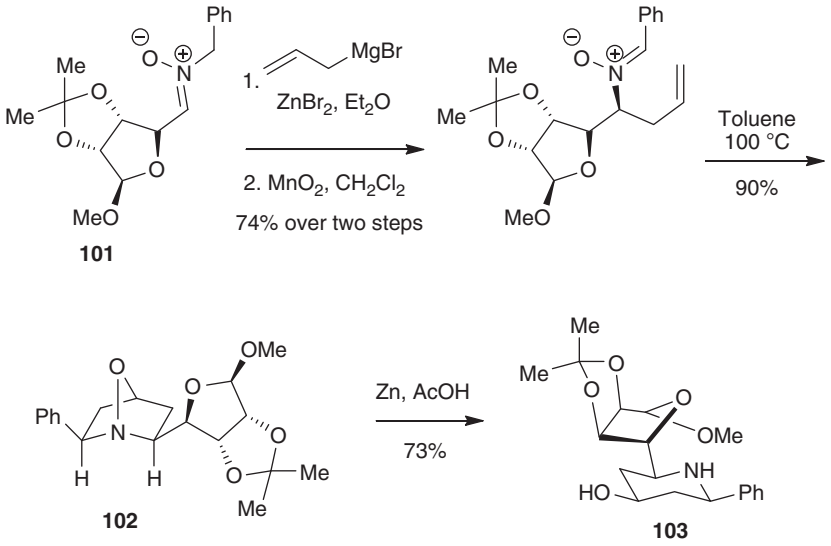
Scheme 32

Homochiral *N*-(alkenylglycosyl)nitrones, prepared by the allylation of *C*-(glycosyl)nitrones and subsequent oxidation, underwent stereoselective intramolecular 1,3-dipolar cycloaddition reactions to furnish cycloadducts that could be used as synthetic precursors of imino disaccharide analogs. For example, D-ribosyl nitrone **101** afforded the cycloadduct **102** which could be converted into a protected 2-furanosyl-4-hydroxy-6-phenyl piperidine **103** in one step (Scheme 33).[56] The stereoselectivity of the allylation reaction was influenced by the nature of the Lewis acid employed. Interestingly, a 2-aza-Cope rearrangement reported for allenyl nitrones[57] was not observed with these substrates.

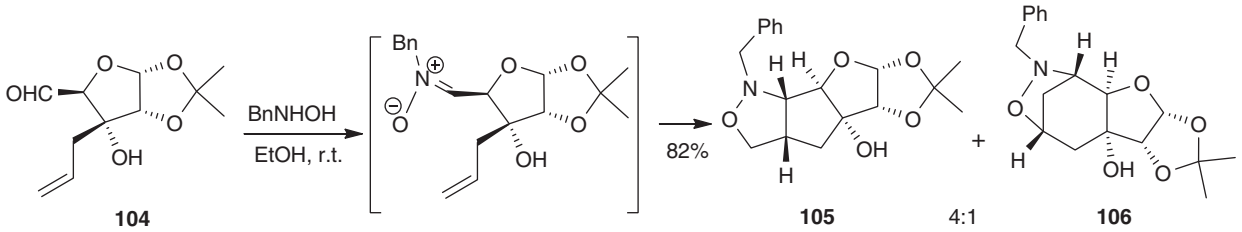
Chiral aldehyde **104** prepared from D-glucose on reaction with *N*-benzylhydroxyl amine furnished the cycloadducts **105** and **106** which are useful intermediates in the synthesis of various bioactive compounds such as enzyme inhibitors, antibiotics, and nucleosides (Scheme 34).[58]

Nitrones prepared from 5-alkenyl proline derivatives **107**, on INAC reaction with benzyl hydroxylamine, afforded azabicyclo [x.3.0]alkane amino acids with heteroatom-substituted side chains. For example, a 9:1 diastereomeric mixture of *exo*-cycloadducts **108** and **109**, which constitute conformationally restricted dipeptide mimics, were obtained from **107** (Scheme 35).[59]

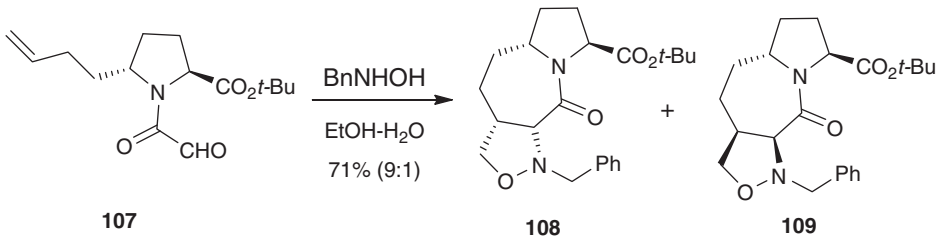
Tricyclic chromenoisoxazolidine derivatives **110** were efficiently prepared from Baylis–Hillman adducts as shown in Scheme 36. The aldehyde-bearing subunit is utilized for the generation of a reactive nitrone **111** and the ensuing stereoselective INAC reaction afforded the tricyclic products **110** in good yields.[60]



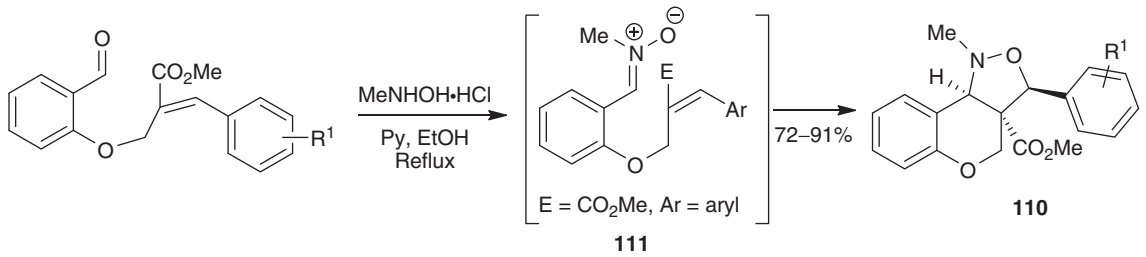
Scheme 33



Scheme 34

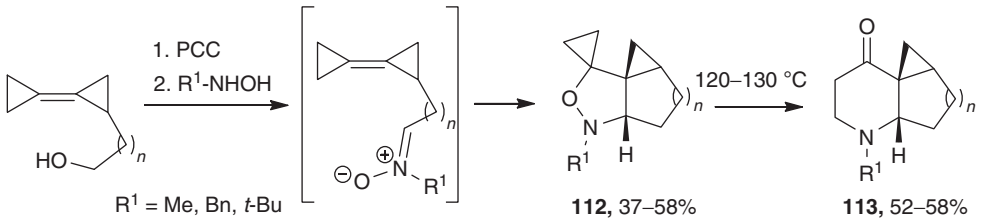


Scheme 35



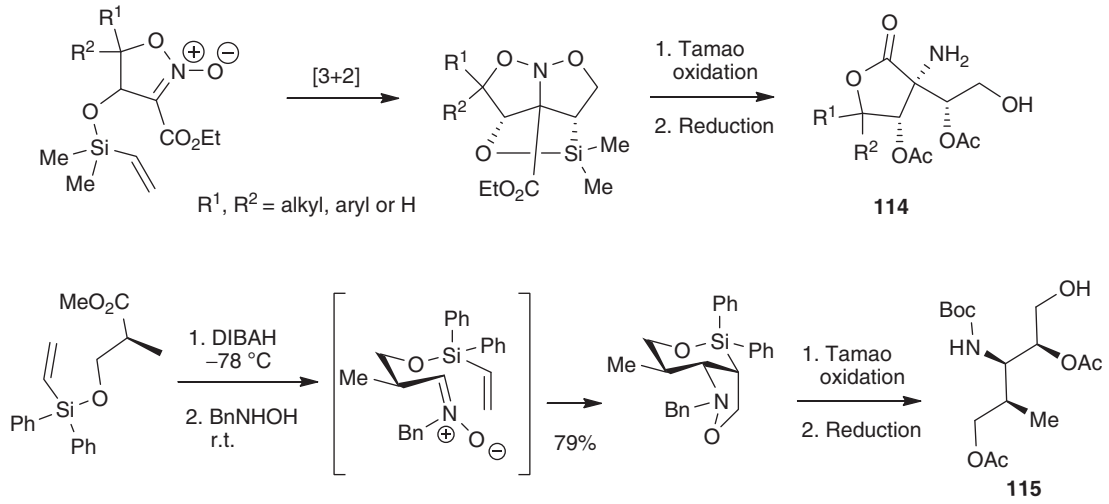
Scheme 36

Nitrones tethered to the cyclopropane ring of bicyclopropylidene derivatives underwent IDC reactions to afford *cis*-fused tricyclic isoxazolidines **112** (Scheme 37). The cycloaddition proceeded with complete regio- and stereoselectivity and the cycloadducts on thermal rearrangement furnished tetrahydropyridone derivatives **113**.[61]



Scheme 37

Vinylsilanes have been employed as dipolarophiles in INAC reactions in which the silicon atom also acts as a tether that controls the regio- and stereoselectivity. The silicon atom can be replaced by an oxygen atom via Kumada–Tamao–Fleming oxidation of the cycloadducts. This strategy has been applied in the synthesis of nonnatural amino acid derivatives **114** as well as stereodefined amino polyols **115** (Scheme 38).[62]



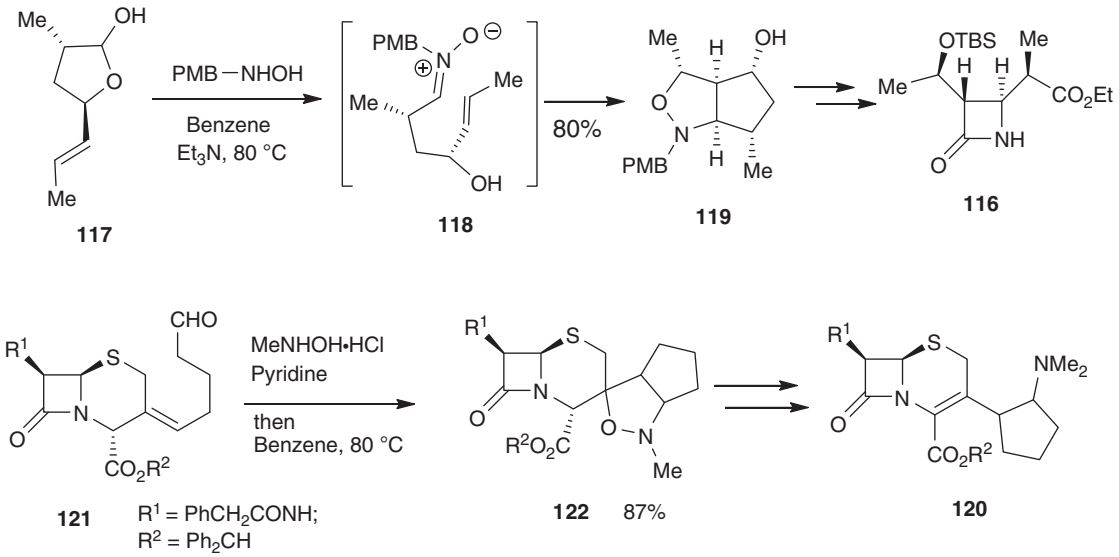
Scheme 38

INAC reactions have been employed for the synthesis and structural modification of antibiotic frameworks. The azetedinone fragment **116** of 1β-methyl carbapenem antibiotic was synthesized from the chiral lactol **117**. The latter was heated with *p*-methoxybenzylhydroxylamine and a base to generate the nitrone **118** which furnished the desired cycloadduct **119** in 80% yield as a single isomer. Further synthetic manipulations were carried out on **119** to assemble the β-lactam **116** (Scheme 39). It is noteworthy that the four contiguous stereocenters present in the target (**116**) were fixed during the cycloaddition reaction.[63] Similarly, cephalosporin derivatives **120** with cyclic substituents at the 3-position were synthesized by means of INAC reactions of 3-alkylidene-4-carboxylic acid derivative **121**. Condensation of the latter with methylhydroxylamine generated the corresponding nitrone and subsequent cycloaddition with the exocyclic olefin afforded a single adduct **122**.[64]

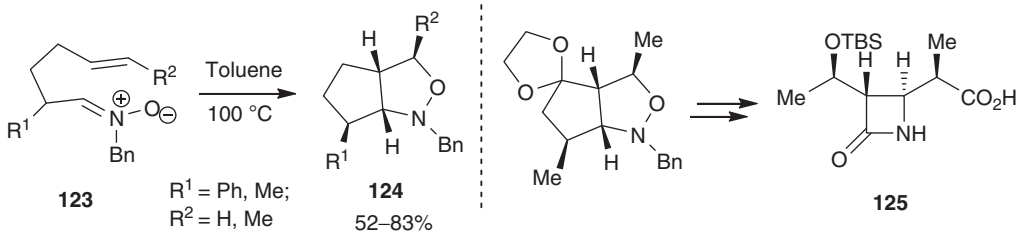
The stereochemical outcome of INAC reactions may be controlled by placing a substituent on C-2 position as exemplified by the case of nitrones **123**. The INAC reactions of the latter afforded only one diastereomer of the 6-substituted and 3,6-disubstituted perhydrocyclopenta[c]isoxazoles **124**. Thus, the C-2 substituent alone controls the formation of three new stereocenters to furnish a cycloadduct with four contiguous stereocenters. Moreover, this INAC reaction was applied in the synthesis of the β-lactam derivative **125** thereby constituting a formal total synthesis of the antibiotic, 1β-methylthienamycin (Scheme 40).[65]

An elegant synthesis of lycopodium alkaloid, (+)-luciduline **126** in 1978 constitutes one of the earliest applications of INAC reactions in natural product synthesis (Scheme 41).[66] In the following years INAC reactions found numerous applications in the total syntheses of natural and nonnatural products including alkaloids, nucleosides, carbasugars, and vitamins.[4]

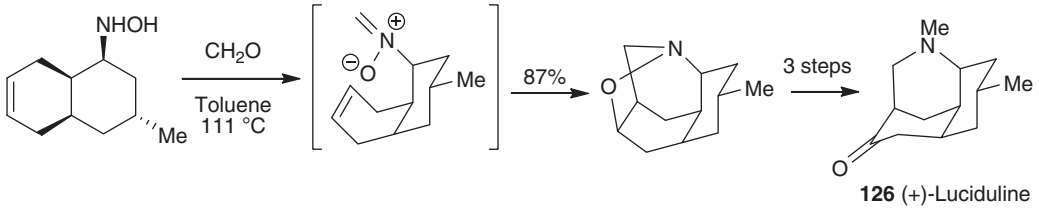
The trail blazing synthesis of (+)-luciduline **126** was followed by a long list of alkaloids that succumbed to total syntheses in which INAC reactions played pivotal roles. The anticancer alkaloid of marine origin, Haouamine A was synthesized from simple



Scheme 39



Scheme 40

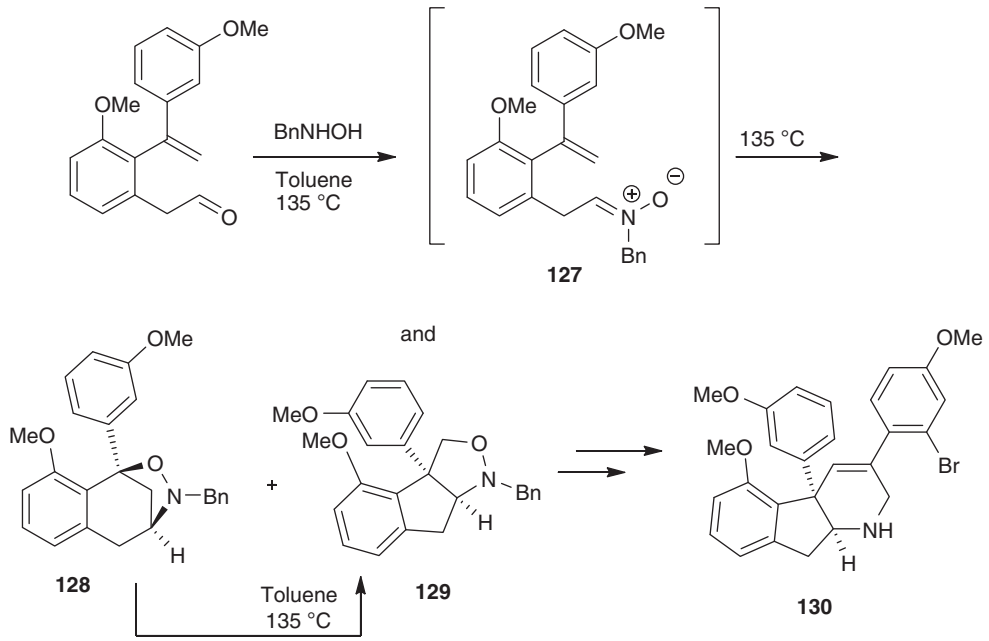


Scheme 41

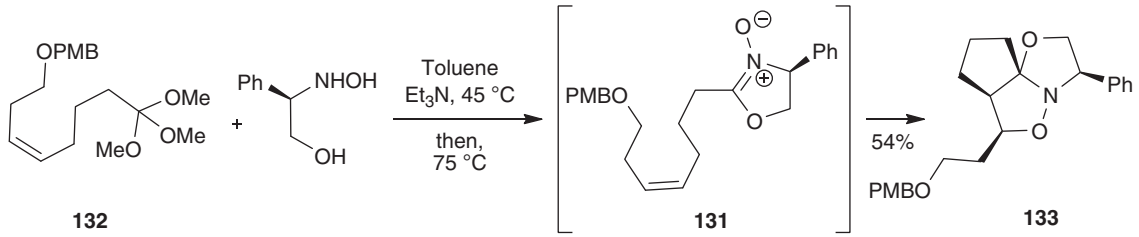
substrates via the INAC reaction of nitrone **127**. The reaction afforded two cycloadducts; however, the kinetically favored cycloadduct **128** could be converted into the desired, more stable isomer **129** by prolonged heating in toluene. This intercoversion presumably involves a thermal cycloreversion and subsequent cycloaddition. The pentacyclic indenotetrahydropyridine derivative **130** was prepared in a few steps from **129**. The former was previously employed in a microwave-assisted intramolecular Diels–Alder reaction to afford Haouamine A (Scheme 42).[67]

Cytotoxic marine alkaloid, pyrinodemin A was synthesized via an asymmetric IDC reaction of an oxazoline *N*-oxide **131**, prepared from the alkenyl *ortho*-ester **132**. This asymmetric cycloaddition afforded the central ring system **133** of the target molecule as a single stereoisomer in good overall yield (Scheme 43).[68]

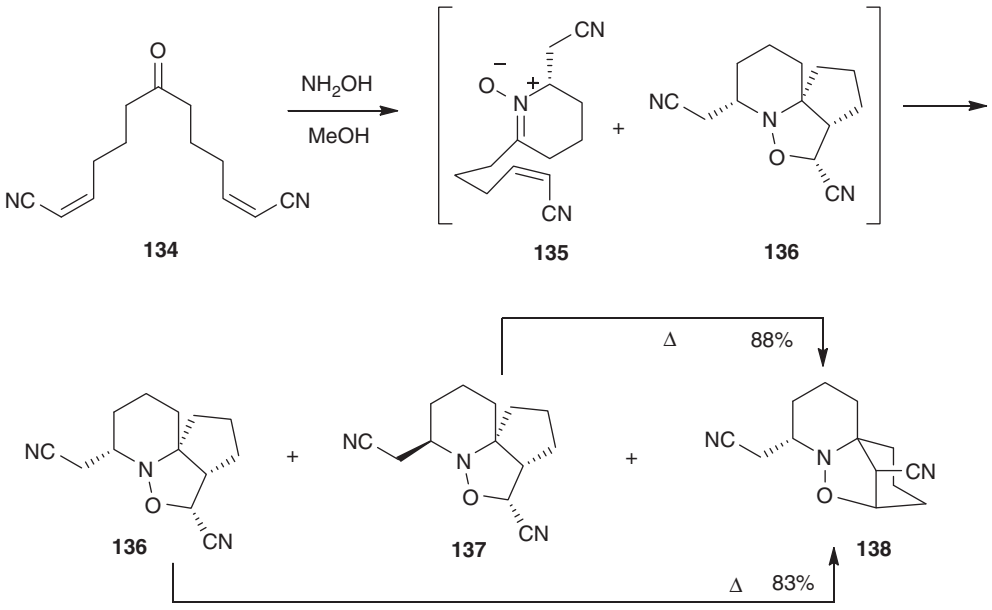
Nitrones may be generated by intramolecular conjugate addition of oximes to Michael acceptors. For example, the oxime derived from **134** underwent aza-Michael addition to the α,β-unsaturated nitrile to generate an equimolar mixture of the nitrone **135** and the kinetically favored cycloadduct **136**. Further heating of this mixture furnished three separable isoxazolidine derivatives **136**, **137**, and **138**. Interestingly, the cycloadduct **136** and the epimer **137** could be independently converted into the thermodynamically favored azaspirocycloundecane cycloadduct **138** which is a known synthetic precursor to all of the known histrionicotoxin alkaloids (Scheme 44).[69]



Scheme 42

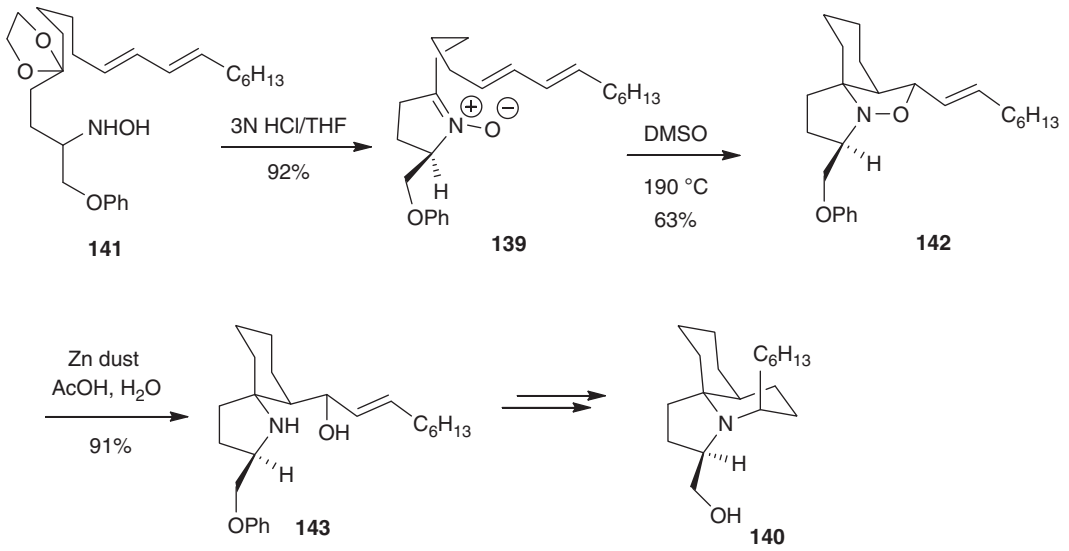


Scheme 43



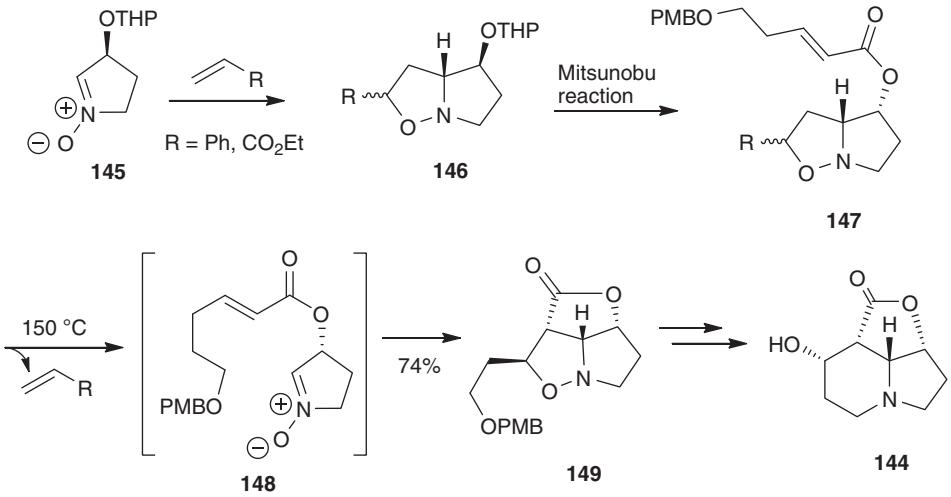
Scheme 44

The INAC reaction of the cyclic nitrone **139** with a tethered 1,3-diene unit formed the key step in the total synthesis of Lepadiformine **140**, a tricyclic indolizidine alkaloid, which exhibits cytotoxic activity toward several tumor strains *in vitro*. A hydrolysis–intramolecular condensation performed on the oxime-acetal **141** generated the stable nitrone **139**. The latter underwent INAC reaction to furnish a single isoxazolidine cycloadduct **142**. The facial selectivity is predicated by the approach of the dipolarophile from the face opposite to the bulky phenoxymethyl group of the cyclic nitrone. The cycloadduct was reduced to the amino alcohol **143**, which was further elaborated into the target lepadiformine **140** (Scheme 45).[70]



Scheme 45

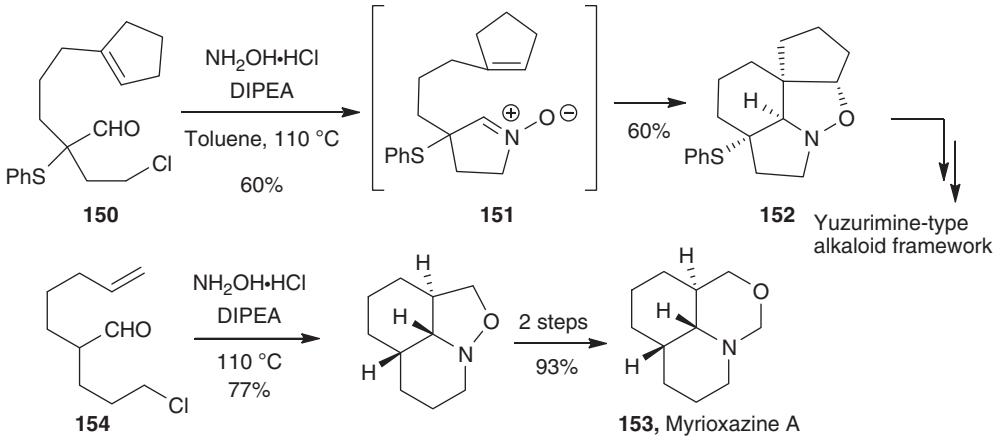
Another instance of the indolizidine framework construction using INAC reaction involves the synthesis of the hydroxylated indolizidines **144**, which are structural analogs of sugars capable of competitively interacting with glycosidases. The pyrroline nitrone **145** derived from L-malic acid was masked as the cycloadduct **146** by a dipolar cycloaddition with ethyl acrylate (or styrene) before attaching the dipolarophilic alkene to the adjacent hydroxyl group. Thermal cycloreversion of **147** to reveal the nitrone **148** and subsequent INAC cycloaddition furnished the isoxazoline derivative **149**. The latter on deprotection, mesylation, and hydrogenolysis afforded the required indolizidine derivative **144** (Scheme 46).[71]



Scheme 46

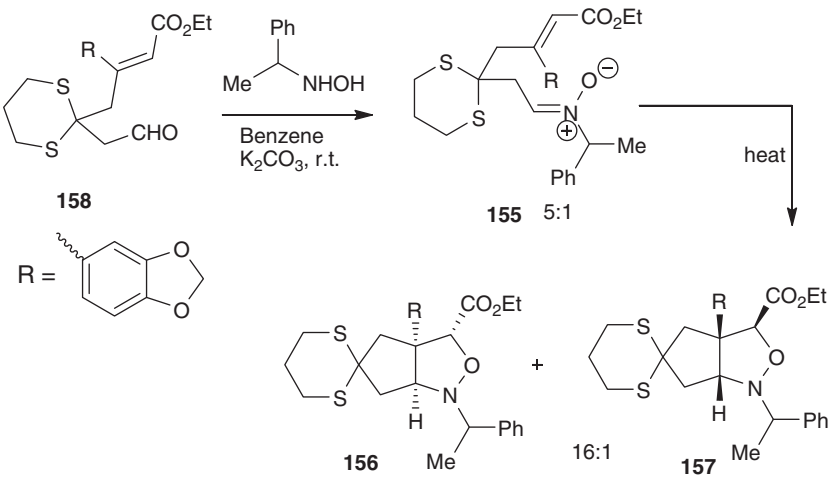
The core ring structure of yuzurimine-type alkaloids has been synthesized via an INAC reaction wherein the nitrone dipole was generated by the addition of hydroxylamine with substituted 4-chlorobutanals **150**. The nitrone **151**, formed via a condensation–nucleophilic displacement sequence, underwent smooth INAC reaction to afford the isoxazolidines **152** that were elaborated to

the required yuzurimine-type frameworks.[72] Antimalarial alkaloid, myrioxazine A **153** was synthesized from **154** via a similar approach (Scheme 47).[73]



Scheme 47

The INAC reaction of the dithioacetal linked nitrone **155** afforded the diastereomeric cycloadducts **156** and **157** in a 16:1 ratio. It is noteworthy that the nitrone **155**, in turn, was formed from **158** as a 5:1 mixture of *cis* and *trans* isomers. The major cycloadduct **156** is an advanced intermediate for the synthesis of pretazettine, a member of the crinine class of amaryllidaceae alkaloids (Scheme 48).[74]

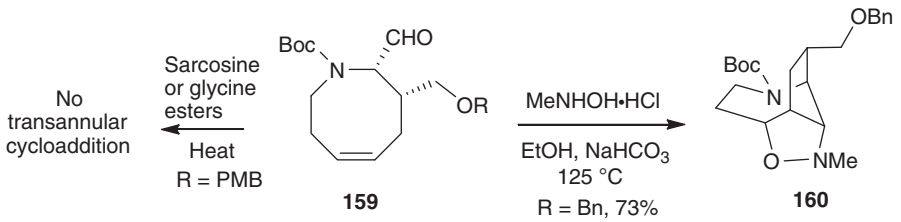


Scheme 48

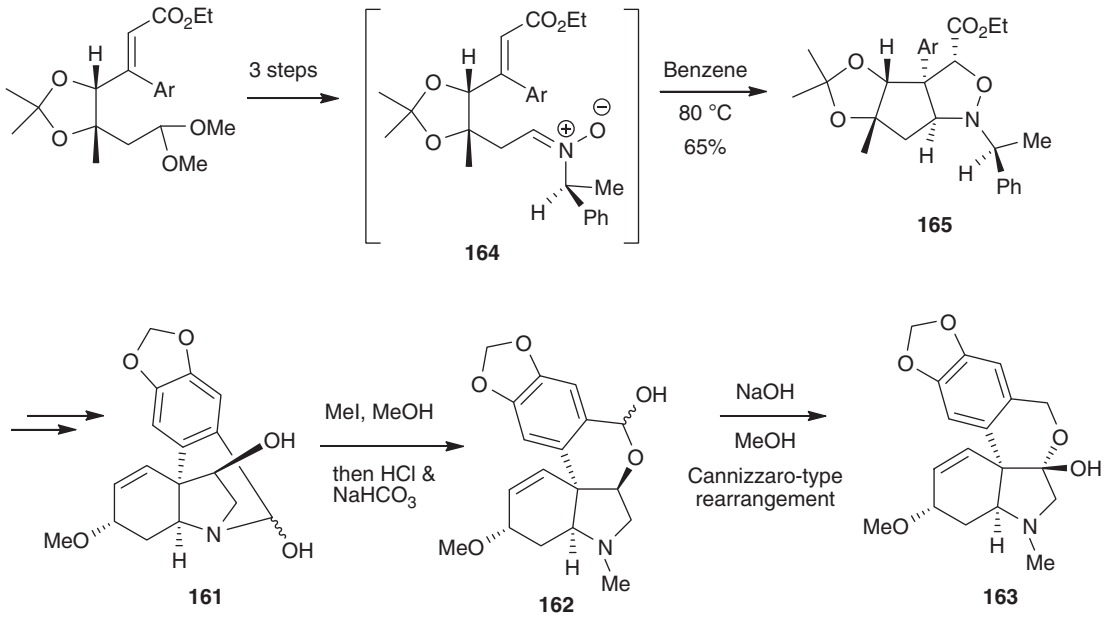
A transannular INAC reaction onto an unactivated alkene in the 8-membered ring of **159** has been reported. Although the objective of the study was to synthesize Saraine alkaloid skeleton, cycloaddition afforded the undesired regioisomer **160** (Scheme 49). Interestingly, an intramolecular azomethine ylide cycloaddition attempted on a similar substrate produced no transannular cycloadduct.[75]

The utility of sugar-derived chiral nitrones in synthesis is demonstrated by the asymmetric syntheses of three related amaryllidaceae alkaloids, (−)-hemanthidine **161**, (+)-pretazettine **162,** and (+)-tazettine **163**. The chiral nitrone **164** synthesized from D-mannose underwent stereoselective thermal INAC reaction to afford the cycloadduct **165**, which was subjected to further synthetic elaborations to afford (−)-hemanthidine **161**. (+)-Pretazettine and (+)-tazettine were sequentially synthesized from **161** by taking advantage of the well-established chemical relationship between these alkaloids (Scheme 50).[76]

The azaspiro[4.5]decane system **166** characteristic of the marine natural products halichlorine and pinnaic acid were synthesized in two independent efforts centered on INAC reactions. The first study, aimed at the synthesis of the core structural unit **166**, made use of an intermolecular aza-Michael addition of the oxime **167** with benzyl acrylate as the nitrone-generating step. INAC reaction of the nitrone **168** with the pendant alkene furnished a single cycloadduct **169** in 92% yield which was transformed into



Scheme 49



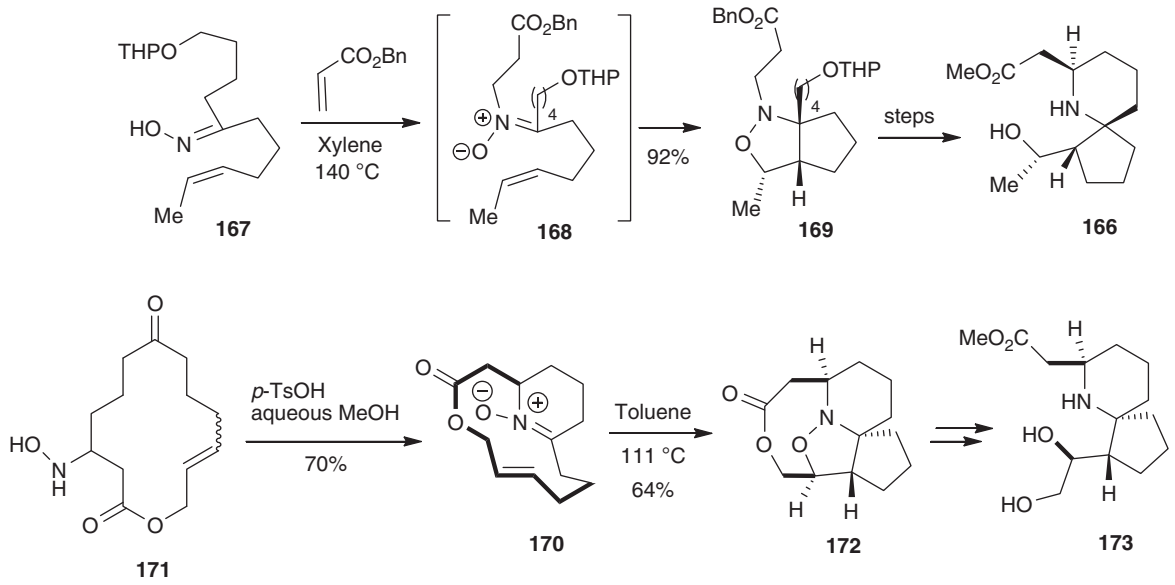
Scheme 50

the target **166** in a few steps.[77] The second study involved an interesting transannular INAC reaction of the stable nitrone **170**, prepared via intramolecular condensation reaction of **171**. The *E*-alkenyl nitrone **170** was stable enough to be chromatographically separated from the minor *Z*-alkene isomer and underwent thermally promoted INAC reaction to afford the cycloadduct **172**. Since the cyclic nitrone is not large enough to allow the nitrone oxygen to pass through the ring, the cycloaddition occurs selectively on the rear face of the endocyclic *trans*-alkene. Synthetic manipulations of the cycloadduct **172** furnished the azaspirocyclic core structure **173** of pinnaic acid (Scheme 51).[78]

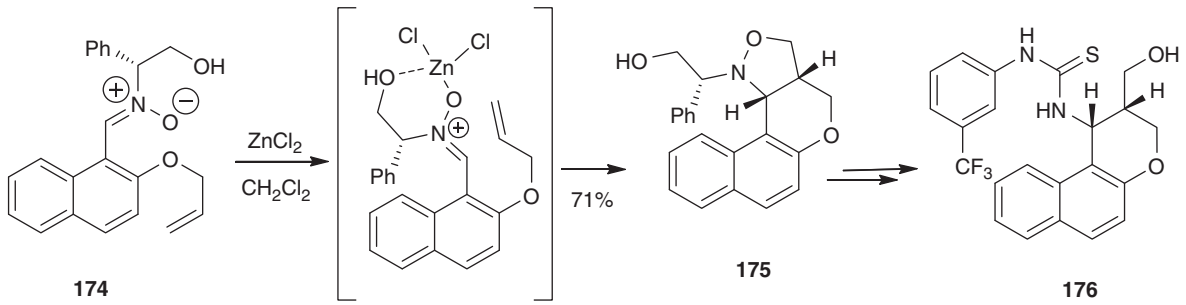
Chiral nitrone **174** endowed with a hydroxyl group on the nitrogen substituent has been employed in a zinc chloride-mediated asymmetric INAC reaction successfully. The Lewis acid chelates with nitrone oxygen and the hydroxyl group on the *N*-substituent and thereby controls the diastereoselectivity of the cycloaddition. The cycloadducts **175** served as precursors for various enantiopure chromane derivatives such as the antibacterial compound **176** (Scheme 52).[79]

Although optically active nitrones are available from the chiral pool of amino acids, sugars, and hydroxy carboxylic acids, they are prone to partial racemization during the cycloaddition reaction and ensuing synthetic manipulations.[80] This issue has been addressed by a domino kinetic resolution–INAC reaction of racemic hydroxynitrones. Thus, the racemic nitrone **177**, on treatment with *Candida antarctica* lipase fraction B (CAL-B) in the presence of an acyl donor **178** which incorporated a tethered dipolarophilic moiety, underwent enantio-differentiating acylation to generate the nitrone **179**. Subsequent INAC reaction afforded the cycloadduct **180** and the enantioenriched unacylated nitrone (*S*)-**177** was left behind (Scheme 54). This elegant approach was also applied in the enantioselective synthesis of (−)-rosmarinecine **181**. The CAL-B-catalyzed acylation followed by facile INAC reaction of racemic **182** furnished the cycloadduct **183** in good yield and enantioselectivity. The latter was then transformed into (−)-rosmarinecine **181** in two steps (Scheme 53).[81]

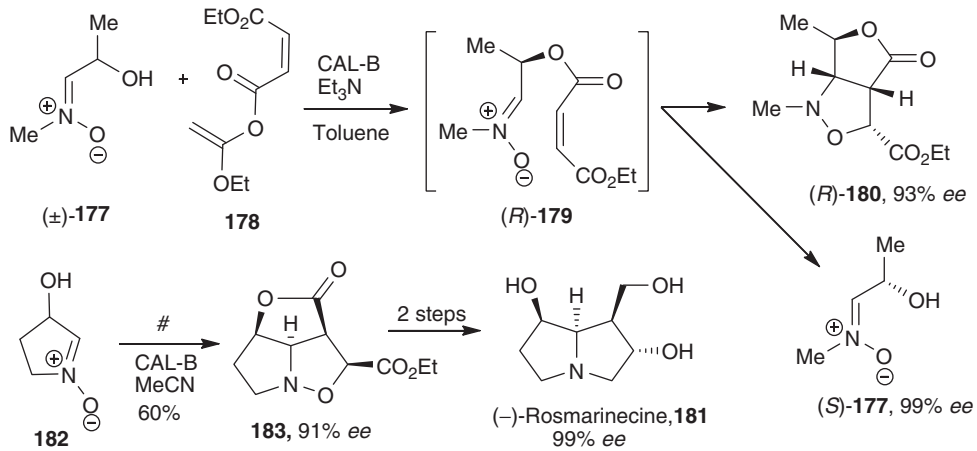
INAC reaction of the alkenyl nitrone **184**, readily obtained from the commercially available chiral oxazinone **185**, afforded the cycloadduct **186** in good yield. The latter functioned as an advanced intermediate in the synthesis of cylindrospermopsin, a hepatotoxin natural product (Scheme 54).[82] A similar approach was followed successfully in the asymmetric total synthesis of the related natural product, 7-epicylindrospermopsin.[83]



Scheme 51

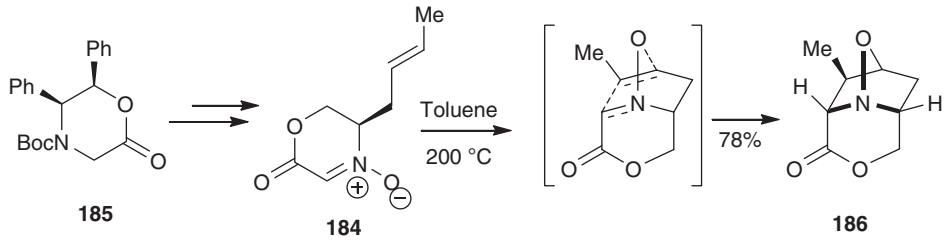


Scheme 52

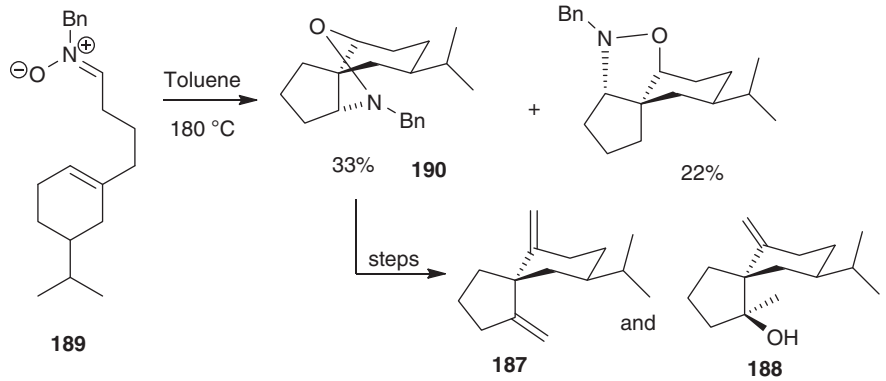


Scheme 53

The ease of reduction of the oxazolidine cycloadducts resulting from INAC reactions render them attractive for carbocyclic construction aimed at terpene synthesis. Two sesquiterpenes, erythroidene **187** and spirojatamol **188**, incorporating a spirobicyclo [5.4]decane framework, were synthesized by employing an INAC reaction of nitrone **189** as the key step. The major cycloadduct **190** endowed with the desired stereochemistry, was further manipulated to furnish the natural products **187** and **188** (Scheme 55).[84]

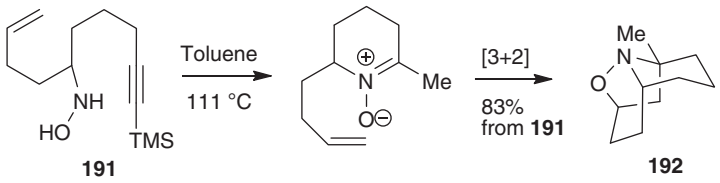


Scheme 54



Scheme 55

Although the condensation of hydroxylamines with aldehydes constitutes the most common method of generation of nitrones, a handful of alternative routes have also been described. In particular, cyclic nitrones may be generated by a hydroxylamine–alkyne cyclization reaction. For example, a cascade cyclization–INAC reaction of **191** with tethered alkenes constitutes a powerful method for the synthesis of tricyclic frameworks **192** associated with alkaloids such as adaline and euphococcinine (Scheme 56).[85]



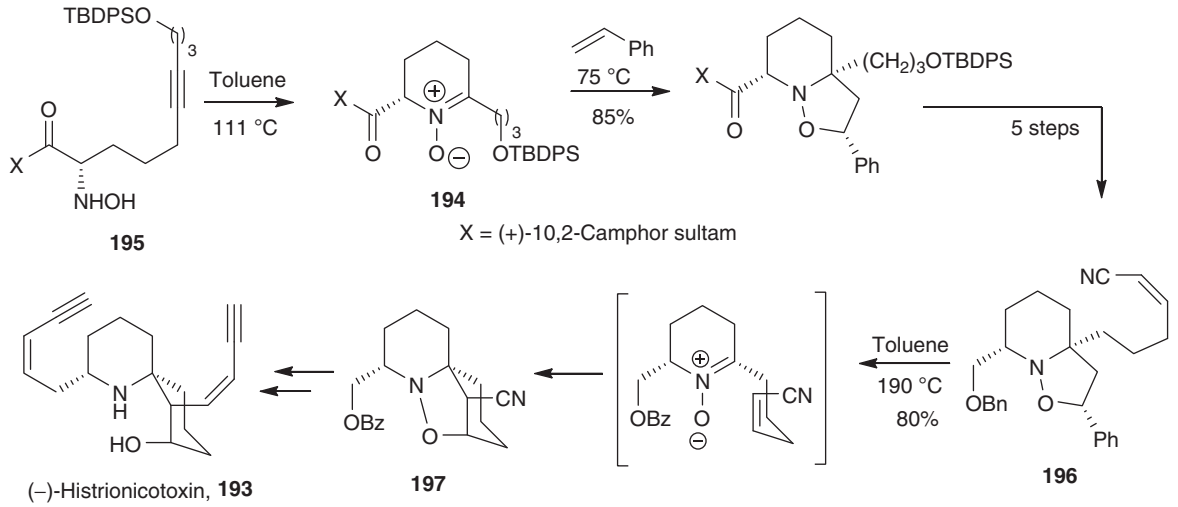
Scheme 56

This method of nitrone generation was applied in an elegant synthesis of (−)-histrionicotoxin **193**, the spiropiperidine alkaloid isolated from the brightly colored poison-arrow frog, *Dendrobates histrionicus*. The cyclic nitrone **194**, accessed from the alkyne **195**, was protected by means of an intermolecular cycloaddition with styrene before side-chain modifications. After installing the α,β-unsaturated nitrile group on the side chain, the isoxazolidine **196** was heated in a sealed tube at 190 °C in toluene to promote the cycloreversion–dipolar cycloaddition sequence. Cycloadduct **197**, resulting from INAC reaction possessed all three chiral centers present in the natural product **193** and was obtained as a single isomer in high yield (Scheme 57).[86]

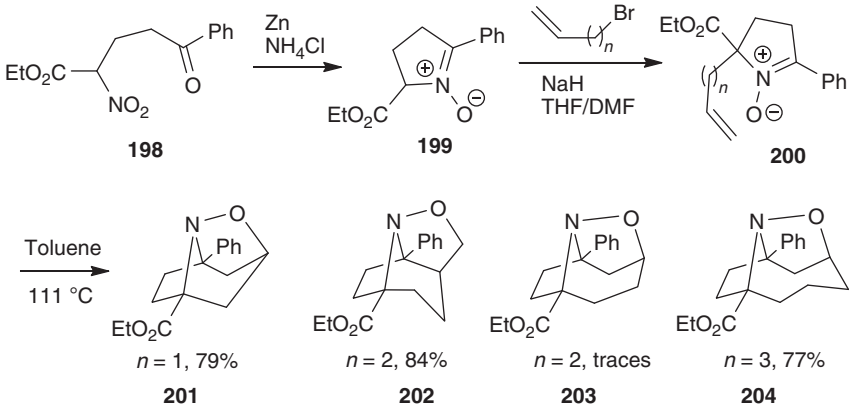
Zn–NH_4Cl reduction of the γ-nitroketone **198** afforded stable cyclic nitrone **199** which could be deprotonated and alkylated at the C-5 position to generate alkenyl nitrones **200**. The latter on refluxing in toluene furnished the cycloadducts **201–204** in good yields as single diastereomers (Scheme 58).[87]

A conjugate addition/IDC cascade was employed successfully in a racemic total synthesis of the piperidine alkaloid, cylindricine C. Oxime **205**, on treatment with 2,3-bis(phenylsulfonyl)-1,3-butadiene **206** generated the transient nitrone **207**, which underwent cycloaddition with the terminal vinylsulfone unit. The 7-oxa-1-azanorbornane cycloadduct **208** was converted into the 4-piperidone **209** by sequential reductions and the natural products was synthesized from the latter in a few steps (Scheme 59).[88] The versatility of this approach is demonstrated by its effective use in the syntheses of alkaloids (±)-perhydrohistrionicotoxin and (±)-2,7,8-*epi*-perhydrohistrionicotoxin[89] from **210** and (±)-yohimbenone from **211**.[90]

Nitrones are also accessible from protected cyanohydrins in a one-pot operation involving diisobutylaluminium hydride (DIBAL) reduction, protonation, and transimination with hydroxylamines. As enantiomerically pure cyanohydrins are easily available, this method has allowed the asymmetric synthesis of fused and bridged isoxazolidines. Thus, the pentenyl nitrone **212**



Scheme 57



Scheme 58

($n=1$) underwent facile INAC reaction at room temperature to afford the fused cycloadduct (**213**). The hexenyl homolog **212** ($n=2$), however, gave the bridged cycloadduct **214** when refluxed in toluene in the presence of $ZnCl_2$ (Scheme 60).[91]

Proline and pipacolic acid derivatives **215** provided convenient access to nitrones **216** via a sequence comprising of amine oxidation, Cope elimination, and subsequent oxidation of the hydroxylamine **217**. These nitrones underwent a subsequent IDC reaction on heating in acetonitrile to furnish spirocyclic lactams or lactones **218** in high diastereoselectivity (Scheme 61).[92]

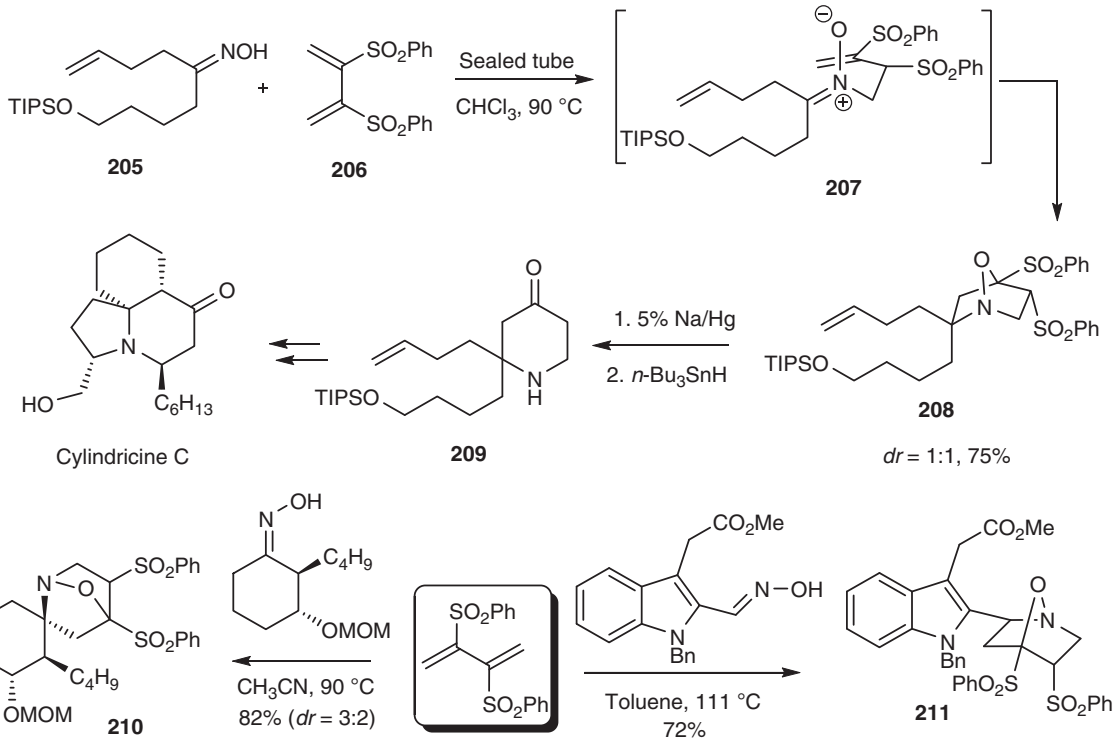
A one-pot oxidation–intramolecular 1,3-dipolar cycloaddition sequence performed on *o*-allylanilines **219** afforded isoxazolidine cycloadducts **220** as single diastereomers. The oxidation of anilines was carried out by the treatment with hydrogen peroxide in the presence of catalytic amounts of sodium tungstate. The cycloadducts **220** on reductive cleavage with Zn/AcOH furnished valuable benzazepine derivatives (Scheme 62).[93]

Finally, an intramolecular homo-[3+2] cycloaddition of nitrones with pendant-activated cyclopropanes has been described. The dipole and cyclopropane may be tethered by alkyl or aryl units and the cyclization is catalyzed by $Yb(OTf)_3$ to afford a variety of bridged 2-oxa-3-azabicylo[2.2.2]octane derivatives **221–222**. Substrates with shorter or longer tether lengths failed to undergo the cycloaddition reaction. Selected examples are presented in Scheme 63.[94]

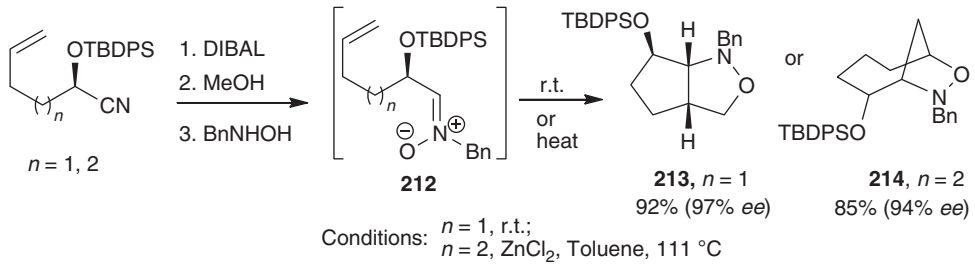
4.21.3.2 IDC Reactions of Nitrones with Alkynes and Allenes

IDC reactions of nitrones with alkynes and allenes are less commonly applied when compared to those of alkenes. Cycloaddition reaction of nitrones with tethered alkynes is known to furnish isolable isoxazoline cycloadducts **223–224** (Scheme 64).[95]

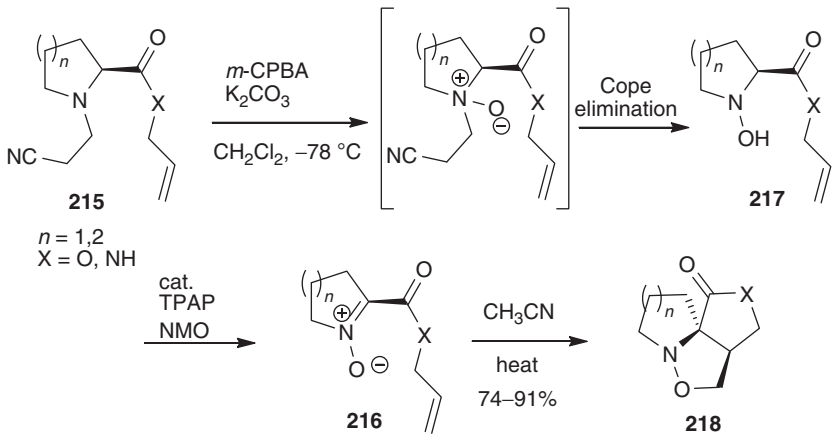
In some cases, however, the cycloadducts were unstable and underwent rearrangement to furnish various products **225**, **226**, or **227** (Scheme 65). IDC reactions of allenyl nitrones are also known to afford corresponding cycloadducts.[95b,96]



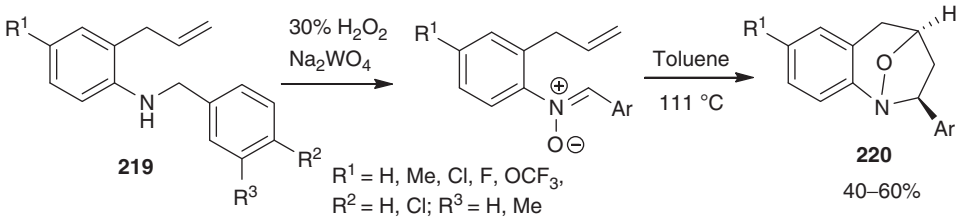
Scheme 59



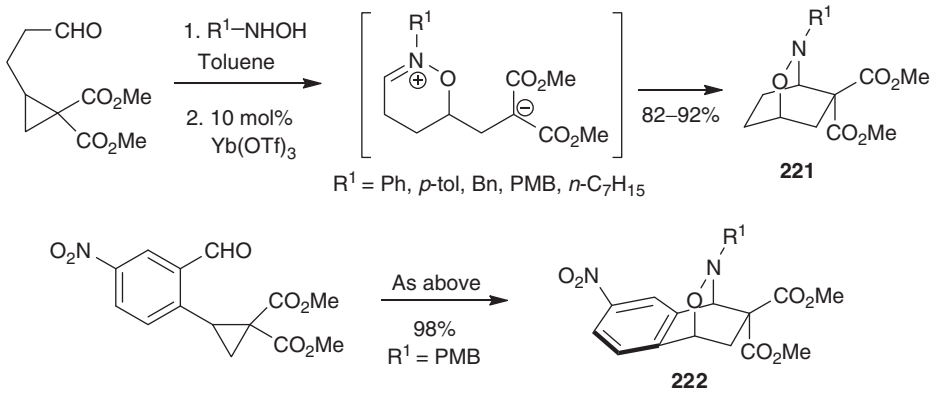
Scheme 60



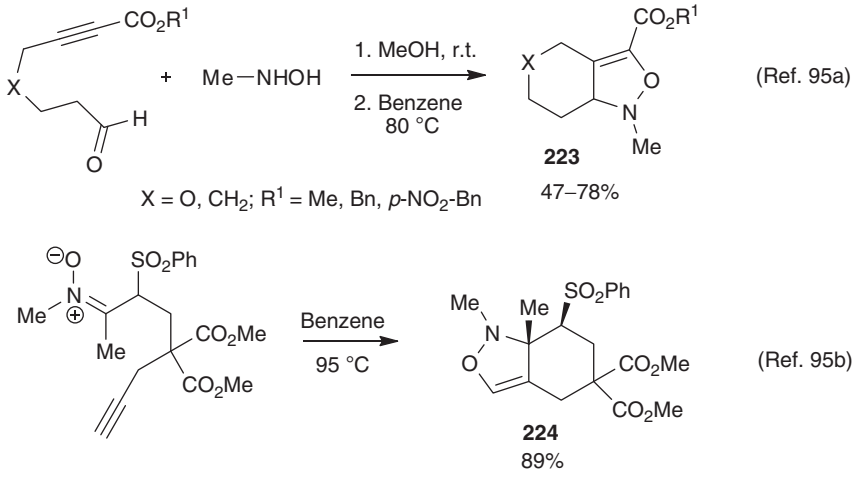
Scheme 61



Scheme 62



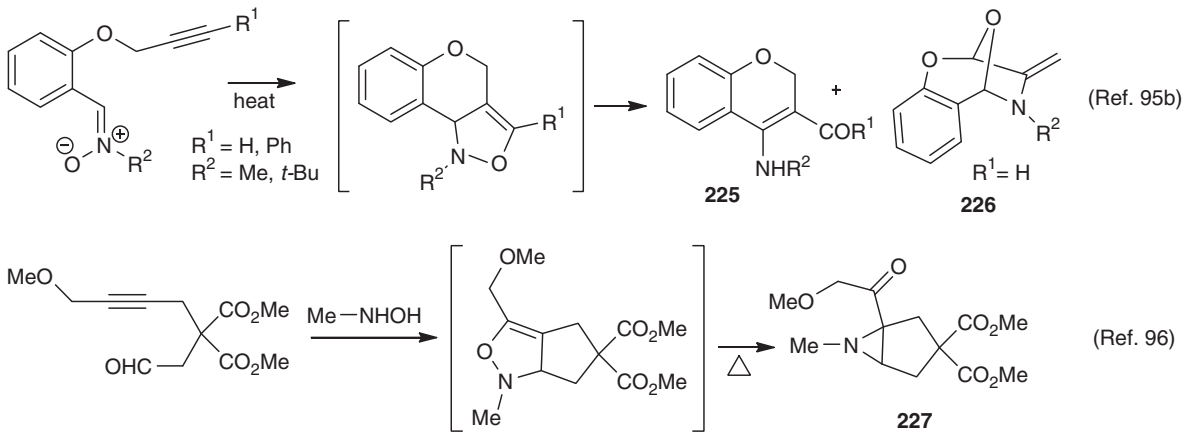
Scheme 63



Scheme 64

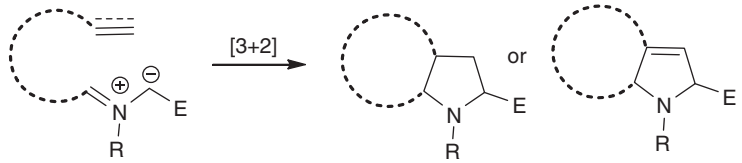
4.21.4 Azomethine Ylides

Ever since the first reaction of its kind was reported in 1976,[97] IDC reactions of azomethine ylides have found numerous applications in the synthesis of natural products, especially alkaloids. Common methods of generation of azomethine ylides include the deprotonation of iminium ions derived from aldehydes and α-amino esters (or acids), fluoride-mediated desilylation of α-silylated imines, interaction of imines with carbenes or carbenoids, and thermolysis or photolysis of aziridines.[98] Dipolar cycloadditions of azomethine ylides lead to pyrrolidines, dihydropyrroles, and pyrroles (Scheme 66). IDC reactions of azomethine ylides have been reported to deliver products incorporating rings of sizes ranging from 4[99] to 20.[100] However, a majority of such reactions describe the formation of small rings (5–7) and provide a fair degree of confidence to practicing chemists to undertake targeted synthetic efforts involving azomethine ylides. It has been demonstrated that the tether length plays a dominant role in



Scheme 65

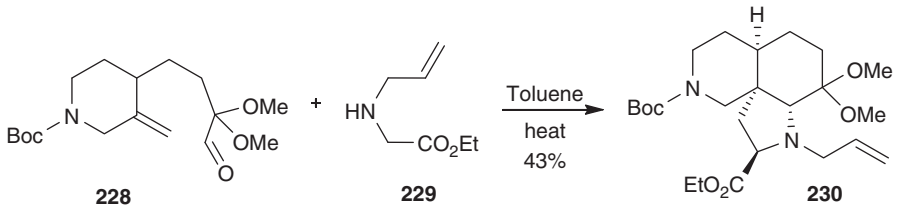
determining the diastereofacial selectivity of IDC reactions.[101] An excellent review covering the literature on the IDC reactions of azomethine ylides up to 2005 is available.[102]



Scheme 66

4.21.4.1 Intramolecular Azomethine Ylide–Alkene Cycloaddition Reactions

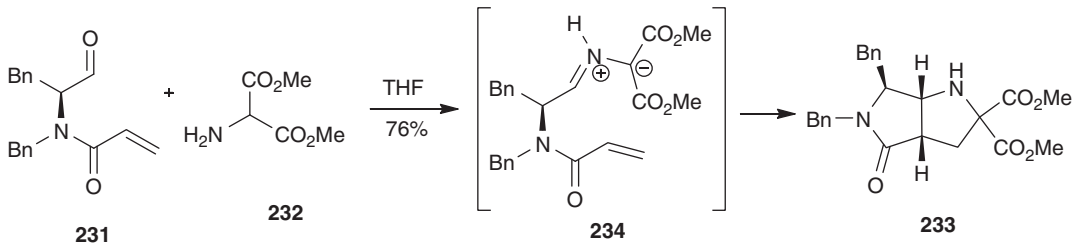
Condensation of amino acid esters with aldehydes is the most widely used method for the generation of azomethine ylides and mediators are seldom required. Medium-sized rings are readily formed even when the dipolarophile is unactivated and the cycloadditions generally proceed with good diastereoselectivity. For example, the IDC reaction of the azomethine ylide formed via the condensation of the aldehyde **228** and *N*-allyl glycine ethyl ester **229** with the exocyclic alkene afforded the tricyclic derivative **230** in moderate yield (Scheme 67). The cycloadduct **230** was employed for the synthesis of ABCE ring system of manzamine alkaloids.[103]



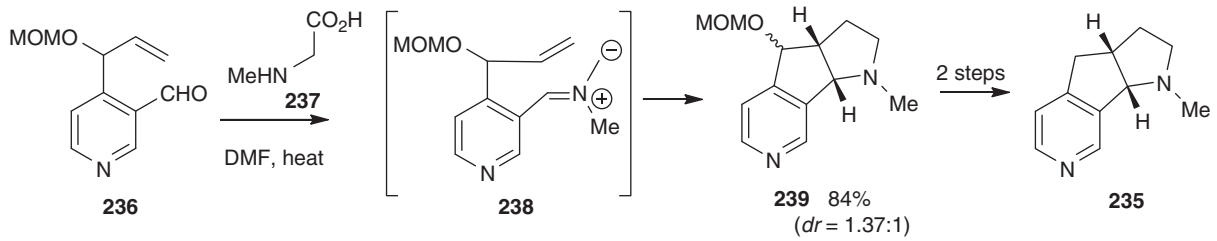
Scheme 67

Reaction of the chiral aldehyde **231** and 2-aminomalonate **232** in THF afforded the cycloadduct **233** via a transient azomethine ylide **234**. Remarkably, the imine formation–azomethine ylide generation–IDC reaction sequence proceeded without any catalyst/mediator at room temperature in THF to furnish a single cycloadduct (Scheme 68).[104]

Structural framework **235** of a potential nicotinic acetylcholine receptor-targeting ligand was assembled by means of an azomethine ylide IDC reaction. The aldehyde **236**, accessible from 3-bromopyridine, was treated with sarcosine **237** in DMF at 100–110 °C to generate the azomethine ylide **238**. The latter was intercepted by the pendant alkene and the ensuing IDC reaction afforded a pair of diastereomers **239** (1.37:1) in 84% yield. The latter was further elaborated to the target compound **235** in two steps (Scheme 69).[105]

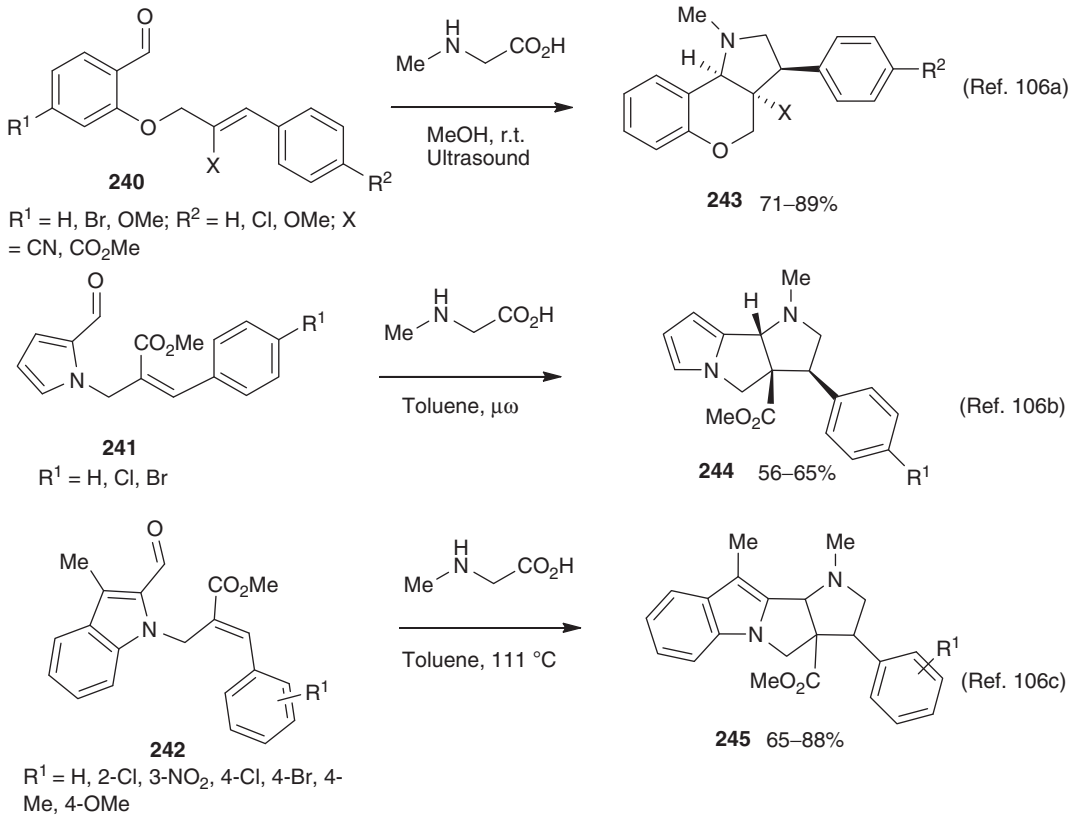


Scheme 68



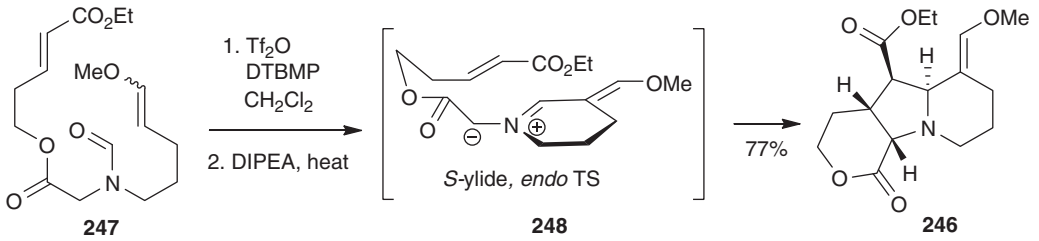
Scheme 69

IDC reactions of azomethine ylides performed on substrates **240–242** derived from Baylis–Hillman adducts generate molecular complexity and diversity in a single operation. The electron-deficient alkene unit present in the Baylis–Hillman adducts functions as the dipolarophile, whereas the azomethine ylide is generated from an aldehyde functionality suitably positioned on an aromatic tether. This strategy has allowed the synthesis of benzo-, pyrrolo-, and indolo-fused polycyclic systems **243–245** from easily accessible starting materials (Scheme 70).[106]



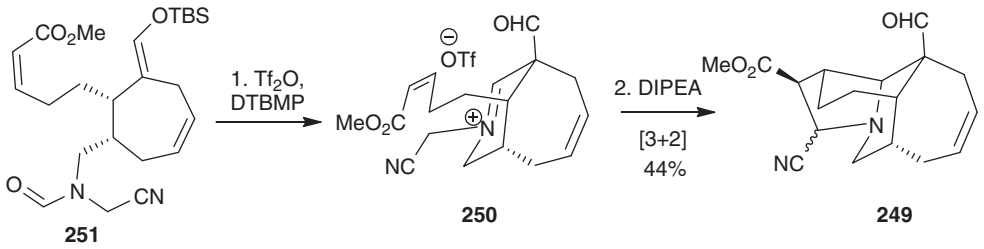
Scheme 70

Cyclic azomethine ylides have been generated by the activation and subsequent Vilsmeier–Haack cyclization of formamides. This method has been used for the synthesis of the tricyclic framework **246** from easily accessible linear substrate **247** (Scheme 71). Here, a suitably placed enol ether moiety functioned as the nucleophile in the triflic anhydride-2,6-di-*tert*-butyl-4-methylpyridine-mediated Vilsmeier–Haack cyclization. Deprotonation of the resultant iminium ion by Hunig's base generated the azomethine ylide **248**. The stereochemical outcome of the IDC reaction indicated that it proceeded via an *endo* transition state **248** in which the ylide adopts an *S*-conformation.[107]



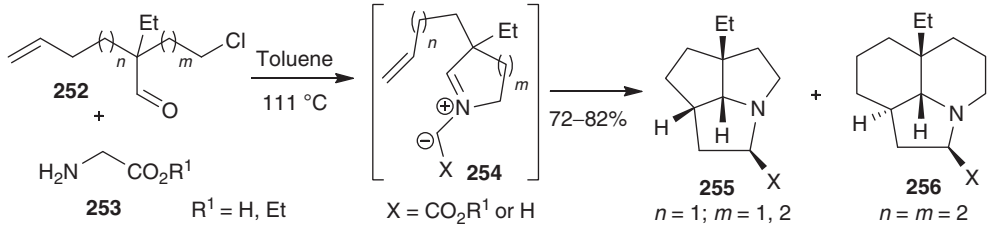
Scheme 71

The protocol described earlier has also been applied in the synthesis of the core structure **249** characteristic of daphniphyllum- and yuzurimine-type alkaloids. The azomethine ylide was generated via the deprotonation of an iminium ion **250** resulting from a triflic anhydride-mediated Vilsmeier–Haack cyclization of formamide **251**. The tetracyclic product **249** was formed in 44% yield as a mixture of diastereomers (Scheme 72).[108]



Scheme 72

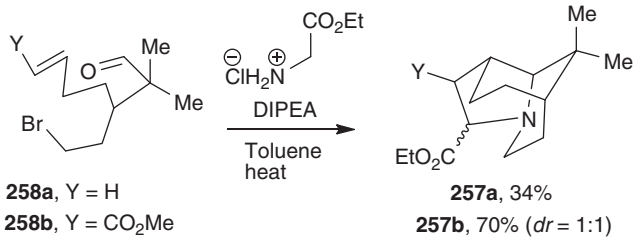
Aldehydes **252**, endowed with a suitably positioned leaving group, on condensation with α-amino esters **253** generate reactive cyclic azomethine ylides **254**. The latter can undergo IDC with tethered alkenes to furnish nitrogen heterocycles **255**–**256** of considerable molecular complexity. This strategy for generating azomethine ylides by condensation–nucleophilic displacement cascade has been applied for the synthesis of a variety of fused nitrogen heterocycles (Scheme 73).[109]



Scheme 73

The same protocol has also been used for the synthesis of the daphniphyllum alkaloid framework **257**. Thus the reaction of δ-bromoaldehyde **258a** (Y=H) with glycine ethyl ester culminated in the formation of the cycloadducts **257a** (Y=H) as a single diastereomer, albeit in low yield (Scheme 74). Activation of the dipolarophile with an electron-withdrawing ester moiety **258b** (Y=CO_2Me) doubled the yield of the product **257b**; however, the diastereoselectivity suffered.[110]

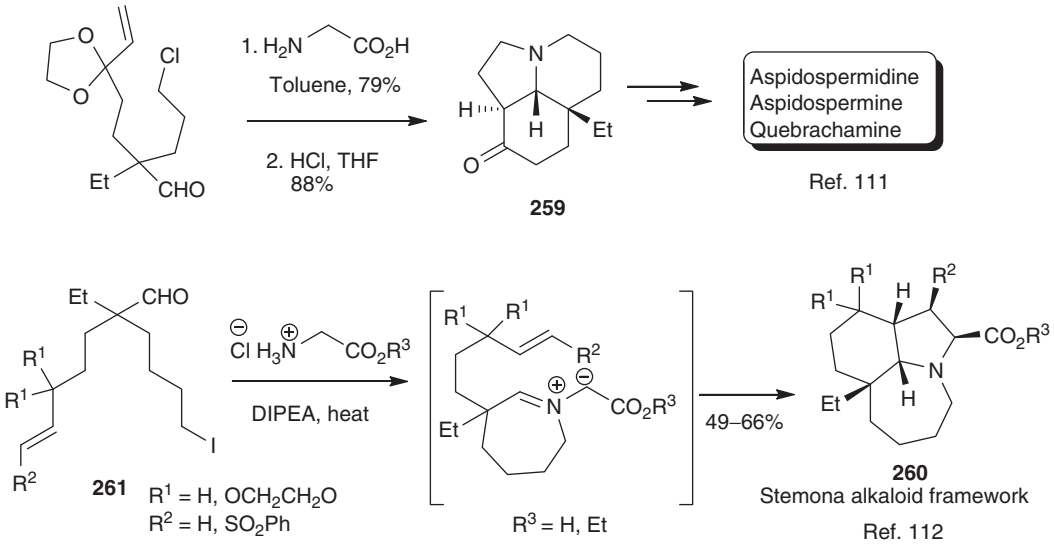
The generality and efficiency of this method of generation of cyclic azomethine ylide is demonstrated by the targeted syntheses of alkaloids scandine, aspidospermine, aspidospermidine, and quebrachamine from the cycloadduct **259**[111] and the facile assembly of stemona alkaloid skeleton **260** from the linear precursor **261** (Scheme 75).[112]



258a, Y = H
258b, Y = CO_2Me

257a, 34%
257b, 70% (*dr* = 1:1)

Scheme 74



261 R^1 = H, OCH_2CH_2O; R^2 = H, SO_2Ph

R^3 = H, Et

260
Stemona alkaloid framework
Ref. 112

Scheme 75

The bridged pyrrolizidine framework **262** characteristic of the alkaloid asparagamine A, was synthesized in a concise manner by employing the IDC reaction of a nonstabilized azomethine ylide as the key step. The dipole **263** was generated by *O*-activation of the vinylogous amide **264** by triflic anhydride followed by desilylation with tetrabutylammonium triphenyldifluorosilicate (TBAT).[113] The oxygenated pyrrolizidine core **265**, similarly accessed from **266**, represents the structural core of the alkaloid (+)-stemofoline (Scheme 76).[114]

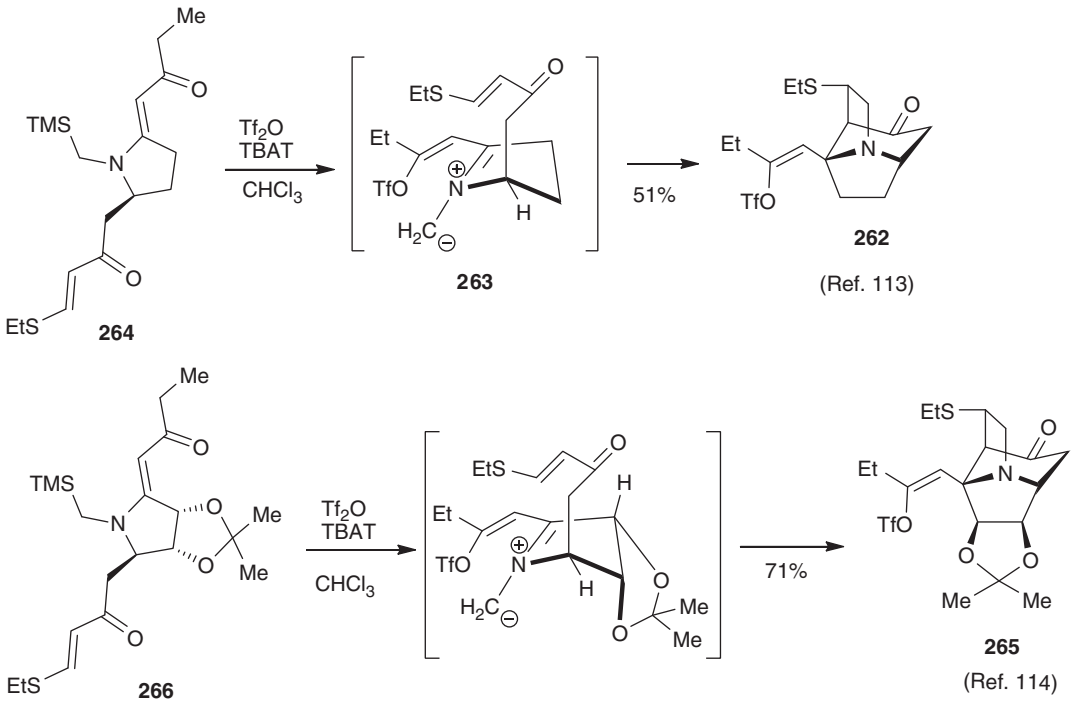
Swern oxidation of the advanced intermediate **267** employed in an attempted total synthesis of *Stemona* alkaloids stemfoline and didehydrostemfoline furnished two tricyclic derivatives **268** and **269**. The transformation proceeds via the azomethine ylide **270** and its subsequent IDC with the pendant alkene (Scheme 77). It is noteworthy that the generation of an azomethine ylide under conditions of Swern oxidation is unprecedented.[115]

The 5,11-methanomorphanthridine core structure of *Amaryllidaceae* alkaloids was prepared by an IDC of a nonstabilized azomethine ylide **271** generated via the sequential double desilylation of the chiral precursor **272** using AgF. Moderate enantioselectivity was observed for the formation of **273**. Related cycloadducts were also formed as single diastereomers from structural analogs of **272** (Scheme 78).[116]

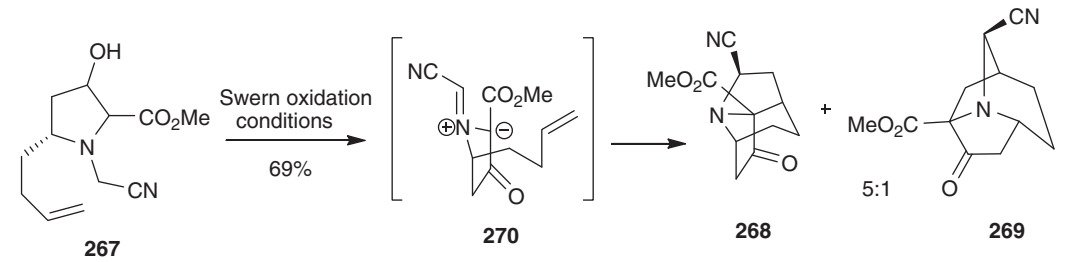
Ylides derived from 2-vinyloxybenzaldehydes **274** allow stereoselective synthesis of tricyclic hexahydrobenzofuro[3,2-b]pyrroles **275** in excellent yields (Scheme 79). The corresponding linearly fused tetracyclic pyrrolizidine and indolizidine could also be accessed by employing amino acids such as proline and pipecolic acids for the azomethine ylide generation.[117]

Azomethine ylide cycloadditions are amenable to asymmetric induction by the use of organocatalysts. Chiral Brønsted acid-catalyzed intramolecular 1,3-dipolar cycloaddition of 4-(2-formylphenoxy)butenoates **276** with various amino esters **277** furnished enantioenriched hexahydrochromeno[4,3-b]pyrrolidine derivatives **278**. The highest selectivity observed was 94% *ee* when 10 mol% of the chiral phosphoric acid **279** was employed as the catalyst (Scheme 80).[118]

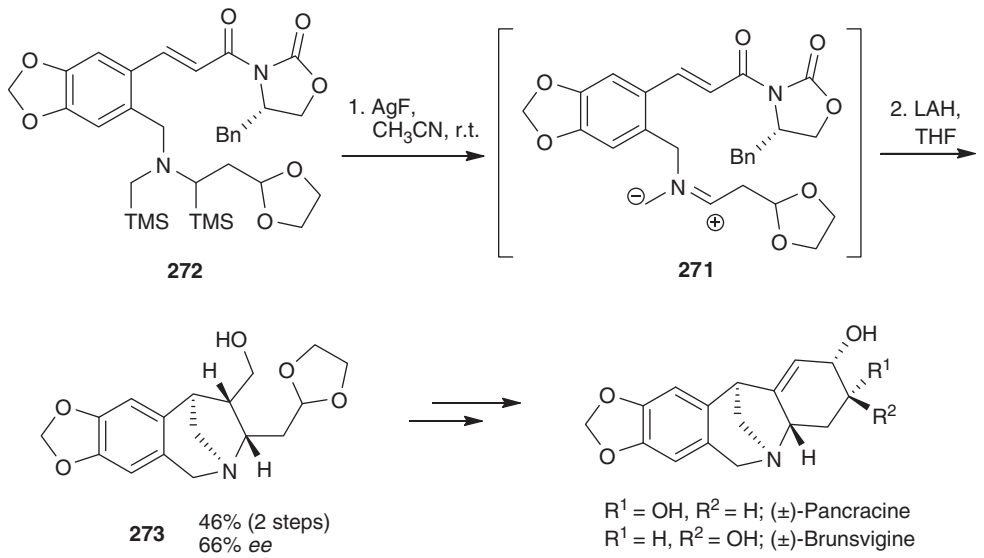
A concise assembly of the tetracyclic ring system **280** found in many indole alkaloids was achieved by an intramolecular azomethine ylide cycloaddition (Scheme 81). The cycloaddition substrates **281**, synthesized from *N*-protected 2-butenylindole-3-carbaldehydes, on treatment with alkylamino esters or amino acids generated the corresponding azomethine ylides that underwent cycloaddition to the pendant unactivated alkenes. A formal total synthesis of the alkaloid desethylibophyllidine was also carried out using this methodology.[119]



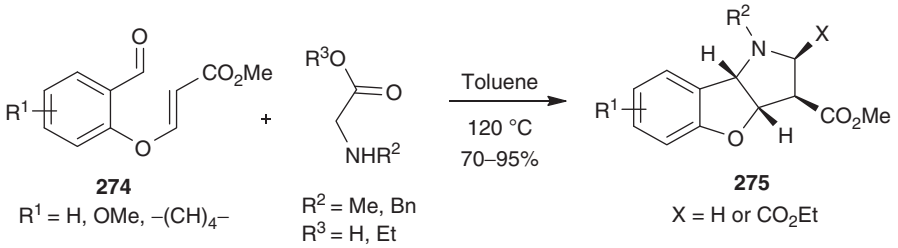
Scheme 76



Scheme 77



Scheme 78

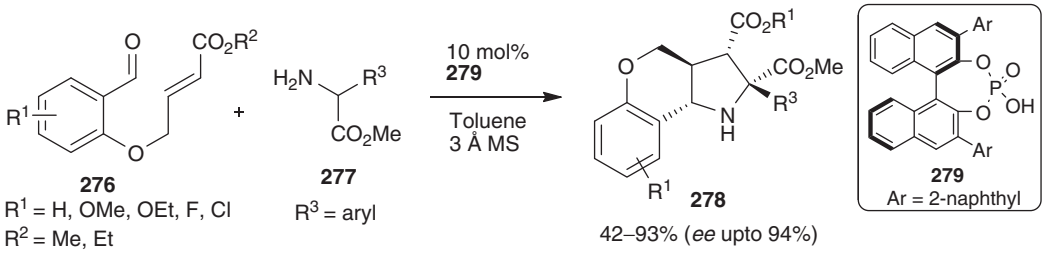


274
R^1 = H, OMe, $-(CH)_4-$

R^2 = Me, Bn
R^3 = H, Et

275
X = H or CO_2Et

Scheme 79



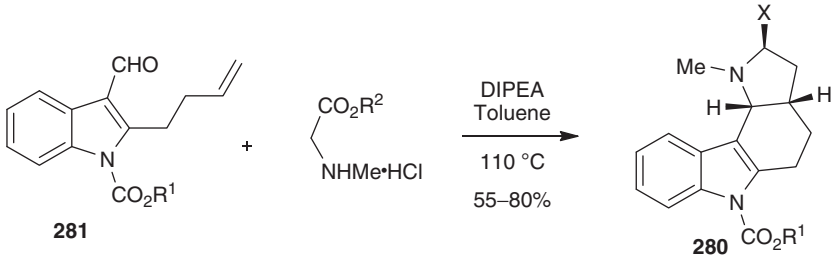
276
R^1 = H, OMe, OEt, F, Cl
R^2 = Me, Et

277
R^3 = aryl

278
42–93% (*ee* upto 94%)

279
Ar = 2-naphthyl

Scheme 80

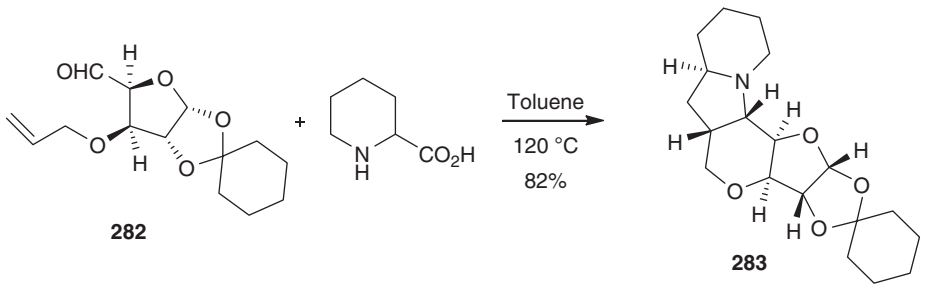


281
R^1 = Me, *t*-Bu; R^2 = H, Et, *t*-Bu

280
X = CO_2R^2 or H (when R^2 = H)

Scheme 81

The carbohydrate-derived *O*-allyl aldehyde **282** underwent intramolecular azomethine ylide cycloaddition reaction with various secondary amino acids to afford furopyrano pyrrolidine/pyrrolizidine/indolizidine derivatives (e.g., **283**) in excellent regio- and diastereoselectivity. A representative example is illustrated in Scheme 82.[120]



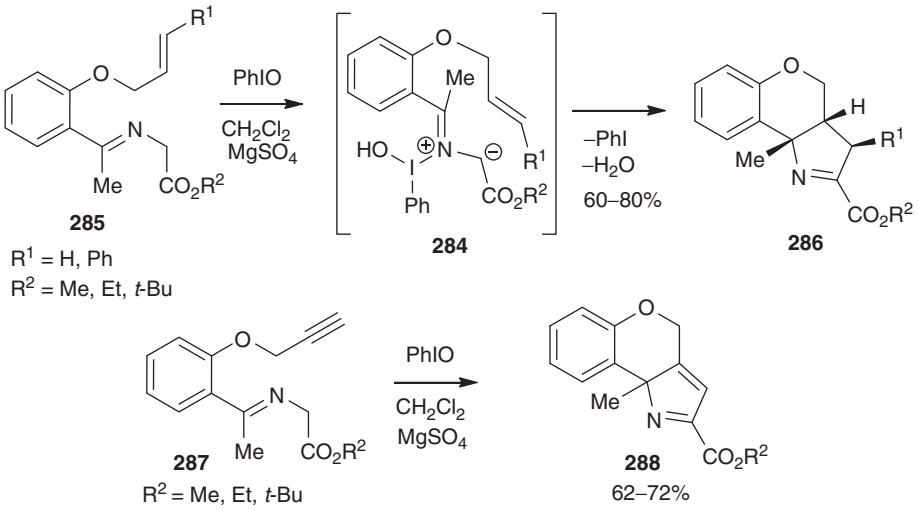
282

283

Scheme 82

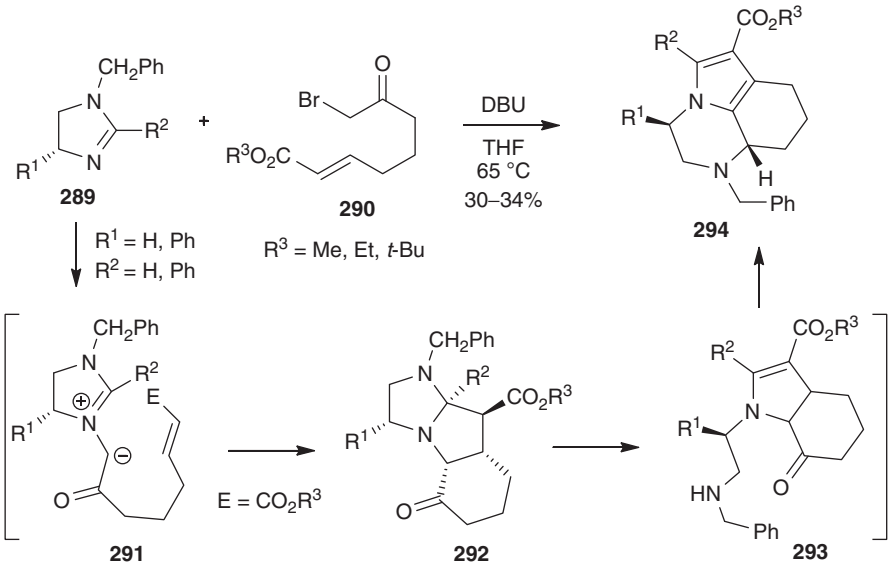
A diastereoselective IDC of azomethine ylides **284** generated by the treatment of ketimines **285** with iodosobenzene culminated in the first synthesis of fused Δ^1-pyrrolines **286**. Stoichiometric amount of iodosobenzene was employed and it served as an oxidant as well as a Lewis acid. Thus, the final products of the reaction are pyrrolines, in contrast to conventional azomethine ylide–alkene cycloadditions, wherein pyrrolidines are formed. Ketimines carrying pendant alkynes **287** also underwent facile

cycloadditions to afford fused 2*H*-pyrroles **288** (Scheme 83). Aldimines, however, underwent dimerization via an intermolecular dipolar cycloaddition to generate imidazole derivatives under the same conditions.[121]



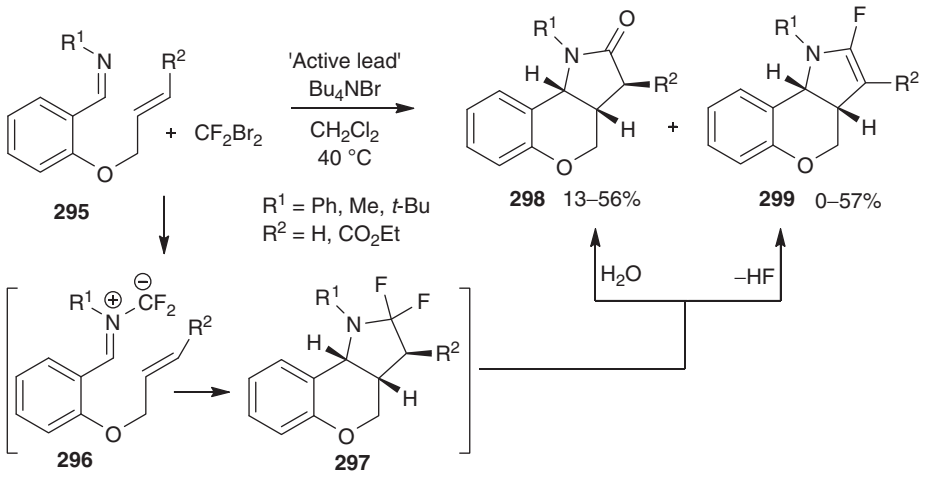
Scheme 83

A remarkable cascade that involves an intramolecular azomethine ylide–alkene dipolar cycloaddition was observed in a low-yielding reaction of 4,5-dihydroimidazoles **289** with alkene-bearing bromomethyl ketones **290**. The ammonium salt formed from **289** and **290** undergoes deprotonation on treatment with DBU to generate the azomethine ylide **291**. The cycloadduct **292**, produced via an IDC reaction of **291**, suffers an eliminative ring opening to furnish the secondary amine **293** and intramolecular condensation of the latter with the keto group and subsequent tautomerization furnishes the final product **294** (Scheme 84).[122]



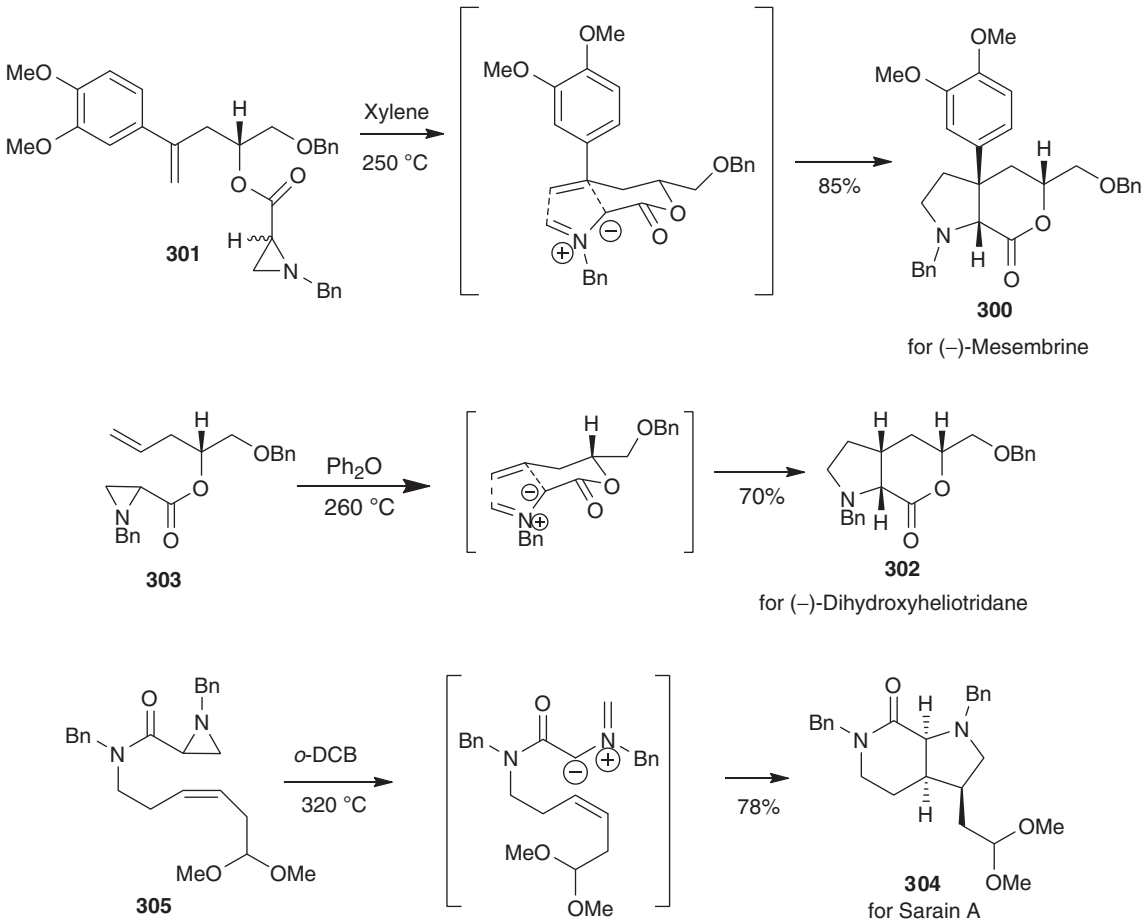
Scheme 84

Azomethine ylides can be generated by the reaction of imines with electrophilic entities such as dihalocarbenes. Interaction of difluorocarbene with Schiff bases **295** carrying a tethered dipolarophilic unit, furnished products derived from the IDC reaction of the corresponding difluoroazomethine ylide **296**. Difluorocarbene was generated by the reduction of CF_2Br_2 by active lead in the presence of tetrabutylammonium bromide. The fluorinated cycloadducts **297** were labile and readily underwent hydrolysis or dehydrofluorination to furnish products **298** or **299**, respectively (Scheme 85).[123]



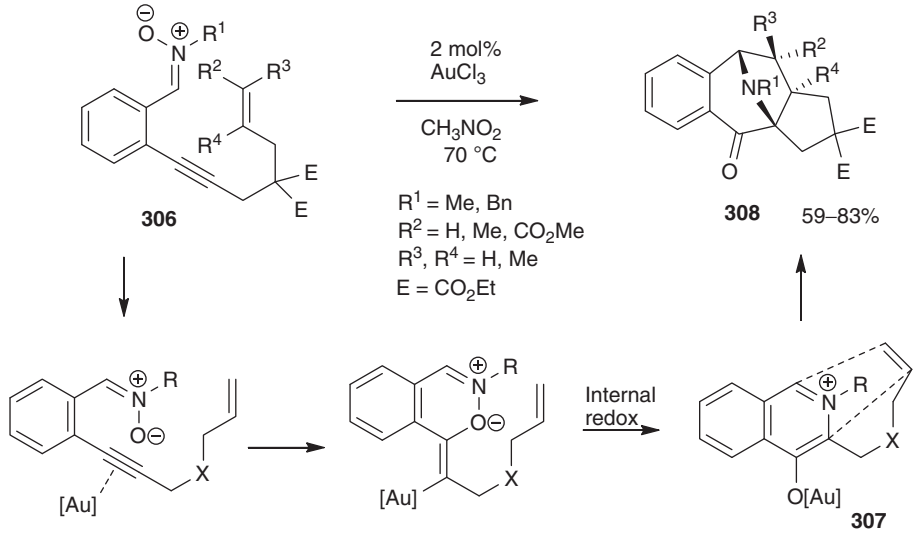
Scheme 85

Thermal or photochemical ring opening of aziridines is a convenient method of azomethine ylide generation.[124] The presence of an electron-withdrawing group on at least one of the aziridine ring carbons is beneficial and hence is a common feature of such transformations. This approach has been followed successfully for the syntheses of alkaloids (−)-mesembrine (from cycloadduct **300** formed from aziridine **301**),[125] dihydroxyheliotridane (from cycloadduct **302** formed from aziridine **303**),[126] and the tricyclic core of sarain A (from cycloadduct **304** formed from aziridine **305**)[127] (Scheme 86).



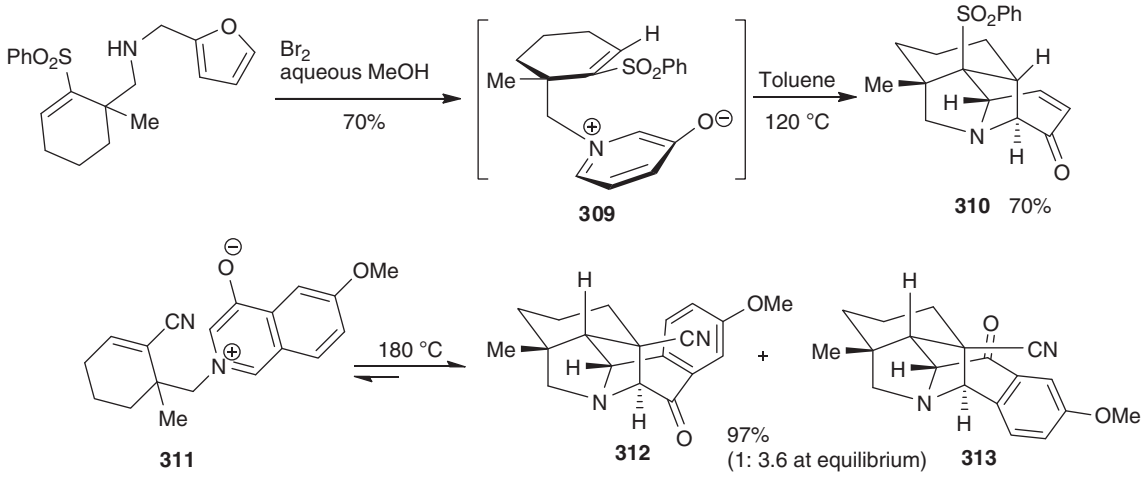
Scheme 86

A novel protocol for the generation of azomethine ylides was reported in 2008. This waste-free method is based on a gold(III) chloride-catalyzed internal redox reaction between a nitrone and an alkyne **306**. The azomethine ylides **307** thus generated reacted with tethered dipolarophiles (alkenes and alkynes) to afford azabicyclo[3.2.1]octane systems **308** (Scheme 87). An auxiliary controlled asymmetric variant of this reaction has also been developed by using chiral hydroxylamines for nitrone generation.[128]



Scheme 87

IDC reactions of 3-oxidopyridinium betaines and 4-oxidoisoquinolinium betaines onto thethered endocyclic alkenes were investigated en route to asymmetric total synthesis of the hetisine alkaloid (+)-nominine. Although the oxidopyridinium betaine **309** underwent thermal dipolar cycloaddition reaction to afford single cycloadduct **310**, reaction of the 4-oxidoisoquinolinium betaine **311** afforded a mixture of cycloadducts **312** and **313**. Remarkably, the cycloaddition is reversible under thermodynamic control and therefore the desired product **312** could be accessed without loss of material by isolation and resubmission of the undesired cycloadduct **313** to the reaction conditions (Scheme 88).[129]

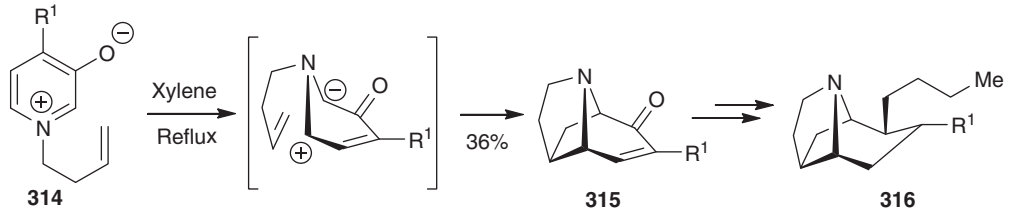


Scheme 88

The IDC of 3-hydroxypyridinium betaine **314**, an azomethine ylide equivalent, with the butenyl side chain at nitrogen furnished a 6-bridged tropenone isomer **315**. The cycloadduct was further elaborated to afford tricyclic cocaine analogs (e.g., **316**) with an extra ring that binds N-8 and C-6, thereby fixing the nitrogen lone pair spatially (Scheme 89).[130]

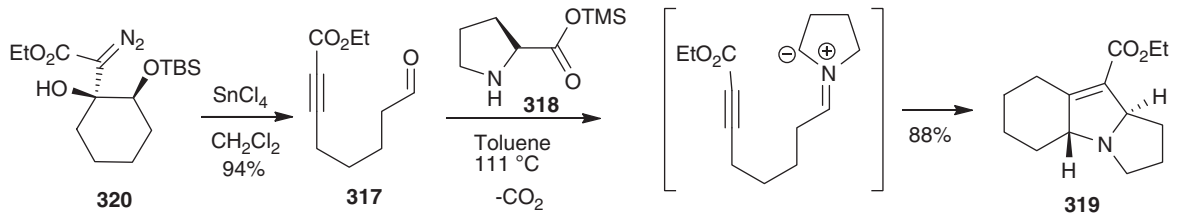
4.21.4.2 Intramolecular Azomethine Ylide–Alkyne Cycloaddition Reactions

Aldehyde **317** tethered to an electron-deficient alkyne on condensation with amino acid silyl ester **318** underwent a stereoselective IDC reaction to afford polycyclic 2,5-dihydropyrrole **319** (Scheme 90). The azomethine ylide precursor, in turn, was conveniently



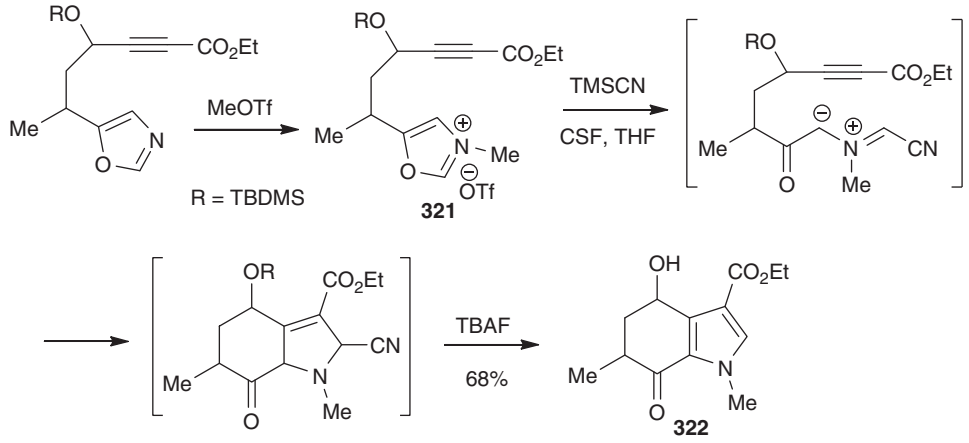
Scheme 89

accessed from the diazoester **320**. As silyl esters of amino acids are more soluble than the corresponding amino acids in organic solvents, it is advantageous to use the former for the generation of azomethine ylides.[131]



Scheme 90

Nucleophilic addition to oxazolium salts are known to result in the formation of azomethine ylides. For example, the addition of cyanide to the oxazolium salt **321** containing an alkynyl tether at 5-position afforded the tetrahydroindolone cycloadduct **322** after aromatization and desilylation (Scheme 91).[132]

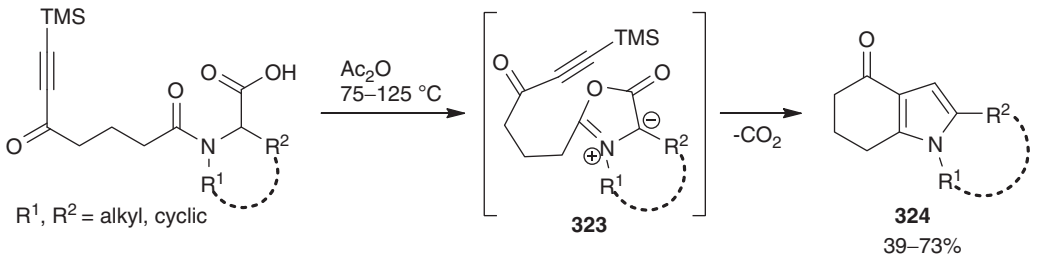


Scheme 91

The dehydration of *N*-acyl amino acids is known to produce mesionic oxazolium-5-oxides, also known as münchnones, which exhibit characteristics of azomethine ylide dipoles.[133] IDC reactions of münchnones **323** tethered with electron-deficient alkynes afforded a variety of oxotetrahydroindoles **324**. Although complete desilylation was observed in the final product, it was found that the trimethylsilyl group on the alkyne facilitated the cycloaddition (Scheme 92).[134]

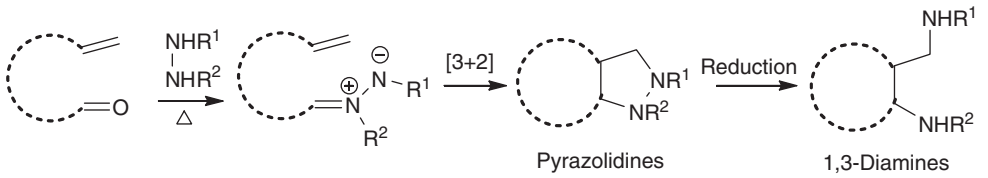
4.21.5 Azomethine Imines

Originally described by Huisgen[1] and studied later in detail by Oppolzer,[135] azomethine imines are generated often by the condensation of substituted hydrazines with carbonyl compounds. Dipolar cycloaddition reactions of azomethine imines with alkenes provide convenient access to pyrazolidine derivatives.[136] Reductive cleavage of the N–N bond of the cycloadducts affords 1,3-diamino derivatives, a commonly encountered feature in synthetic endeavors involving azomethine imines (Scheme 93).[137] Applications of IDC reactions of azomethine imines are fewer in number when compared to that of closely related dipoles such as



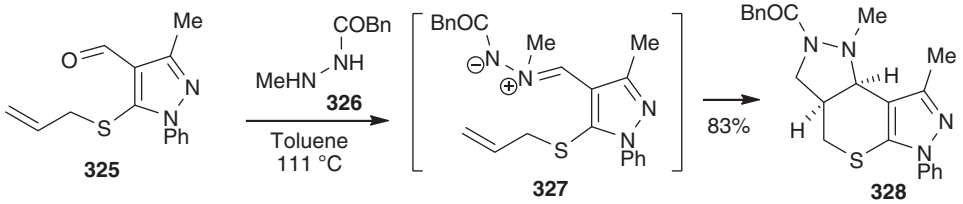
Scheme 92

azomethine ylides or nitrones. In the IDC reactions of azomethine imines, dipolarophiles may be tethered to the carbonyl or hydrazine component.



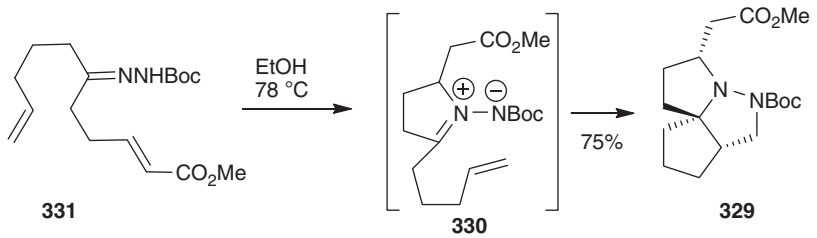
Scheme 93

Aldehyde **325**, reacted with *N′*-methyl-2-phenylacetohydrazide **326**, to generate the azomethine imine **327** which underwent facile IDC reaction to afford the *cis*-fused pyrazolidine (Scheme 94).[138]



Scheme 94

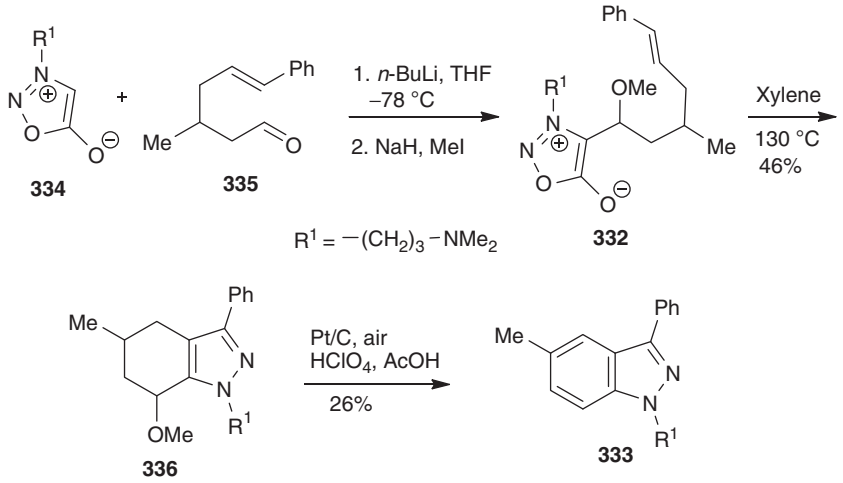
Tricyclic pyrazoline derivative **329** has been synthesized by the IDC reaction of the cyclic azomethine ylide **330**. The dipole was generated via an intramolecular hetero-Michael addition of the hydrazone to the electron-deficient alkene in **331** and subsequent proton transfer. The cycloadduct **329** was obtained as a single diastereomer in 75% yield (Scheme 95). Reductive cleavage of the N–N bond in **329** and subsequent transformations afforded a differentially protected trifunctional spirodiamino acid scaffold, which is of potential utility in combinatorial synthesis.[139]



Scheme 95

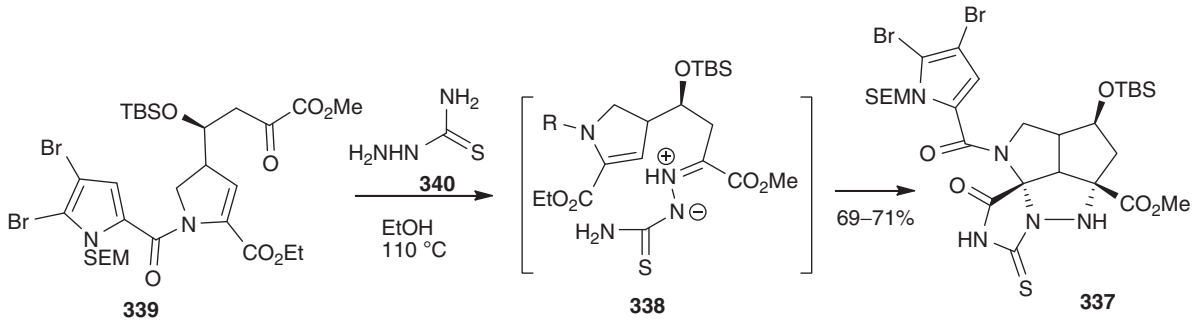
IDC reaction of 3-alkyl sydnone **332**, which serves as a masked azomethine imine, was a crucial step in the synthesis of the antidepressant drug candidate, FS-32 **333**. An alkenyl side chain was attached to the sydnone **334** by an aldol reaction with the aldehyde **335** to afford a mixture of diastereomers. The methyl ether **332** derived from the aldol product was heated in xylene at 130 °C to afford the tetrahydroindazole derivative **336** in 46% yield via an IDC reaction–decarboxylation sequence (Scheme 96).

The cycloadduct **336** was subjected to aerobic oxidation in the presence of Pt/C, $HClO_4$, and acetic acid to arrive at the target compound, FS-32 **333**.[140]



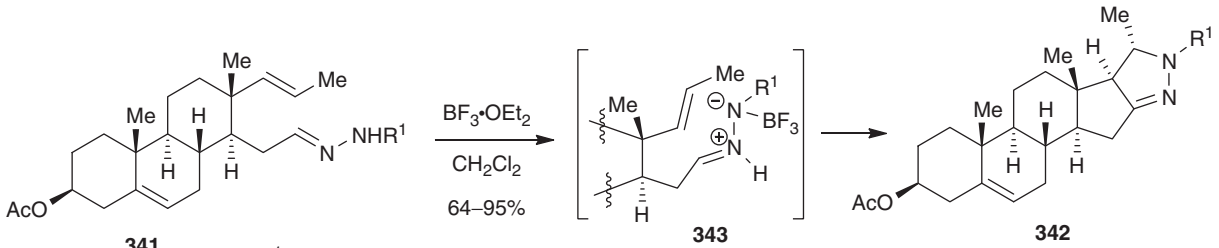
Scheme 96

The synthesis of triazacyclopenta[*cd*]pentalene framework **337**, characteristic of guanidine alkaloids such as palaúamine and styloguanidine was achieved by the IDC reaction of azomethine imines. The dipole **338** was generated by the condensation of dihydropyrrole *α*-ketoester **339** with thiosemicarbazide **340** (Scheme 97). It is noteworthy that the annulation reaction exhibits a good degree of functional group tolerance.[141]



Scheme 97

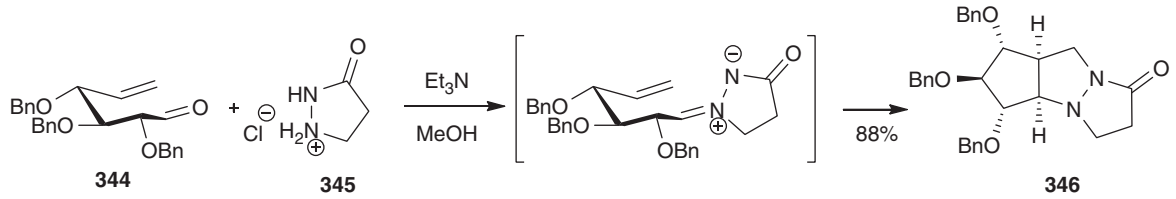
Phenylhydrazones **341** derived from an unsaturated D-*seco*-pregnene aldehyde carrying an alkenyl side chain, underwent intramolecular 1,3-dipolar cycloaddition on treatment with $BF_3{\cdot}OEt_2$ to afford pyrazoline-fused D5-androstene analogs **342** (Scheme 98). This oxidative cycloaddition proceeded smoothly under mild conditions in good to excellent yields and stereoselectivity via the corresponding azomethine imine intermediates **343**.[142]



R1 = Ph, 4-Cl–C6H4, 4-Me–C6H4
4-OMe–C6H4, 4-NO2–C6H4, 4-CF3–C6H4

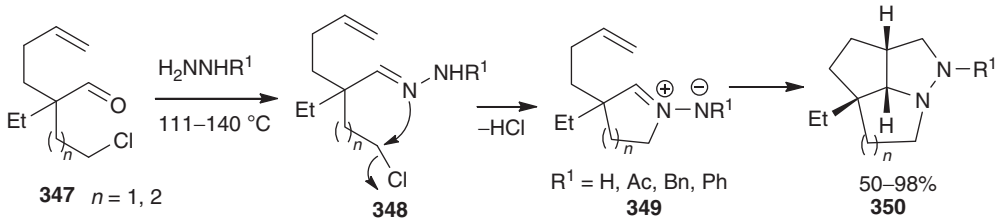
Scheme 98

Sugar-derived hexenals **344** and pyrrazolidin-3-ones **345** undergo condensation in the presence of triethylamine to furnish diazatriquinane derivatives **346** in excellent yield and stereoselectivity. A typical example is portrayed in Scheme 99. 5-Substituted pyrrazolidinones as well as various protecting groups on the hydroxyl groups of the sugar-derived aldehyde are tolerated.[143]



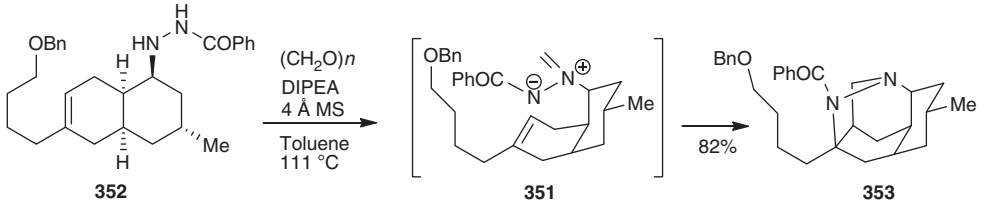
Scheme 99

Aldehydes **347** endowed with a tethered leaving group at a favorable distance serve as useful precursors for azomethine ylides on condensation with hydrazines. The hydrazones **348** undergo intramolecular nucleophilic displacement followed by deprotonation to generate the azomethine ylide intermediates **349**. Facile IDC ensued to afford tetrahydropyrazole products **350** as single diastereomers in excellent yields (Scheme 100).[144]



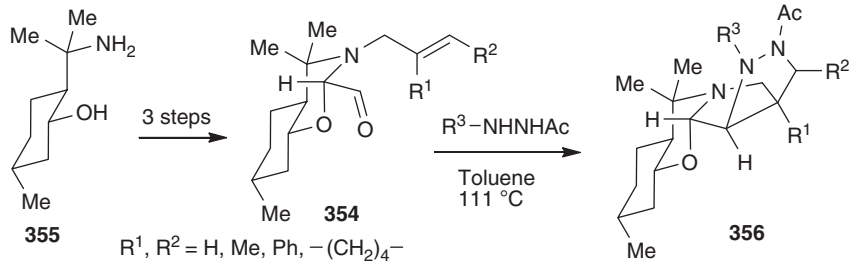
Scheme 100

The first total syntheses of (+)-nankakurine A and (+)-nankakurine B were accomplished by employing the IDC reaction of azomethine ylide **351** as the key step. Reaction of the hydrazide **352** with paraformaldehyde in the presence of base and powdered molecular sieves afforded the tetracyclic pyrazolidine product **353** in 82% yield (Scheme 101). The IDC reaction was completely regio- and stereoselective and the cycloadduct **353** was converted into the natural products in a few steps.[145]



Scheme 101

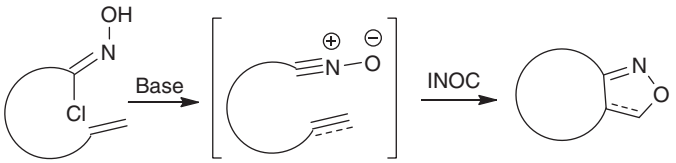
Azomethine imines generated by the condensation of substituted hydrazines with chiral aldehydes **354** derived from (−)-8-aminomenthol **355** underwent stereoselective IDC reactions to afford tetracyclic products **356** (Scheme 102).[146]



Scheme 102

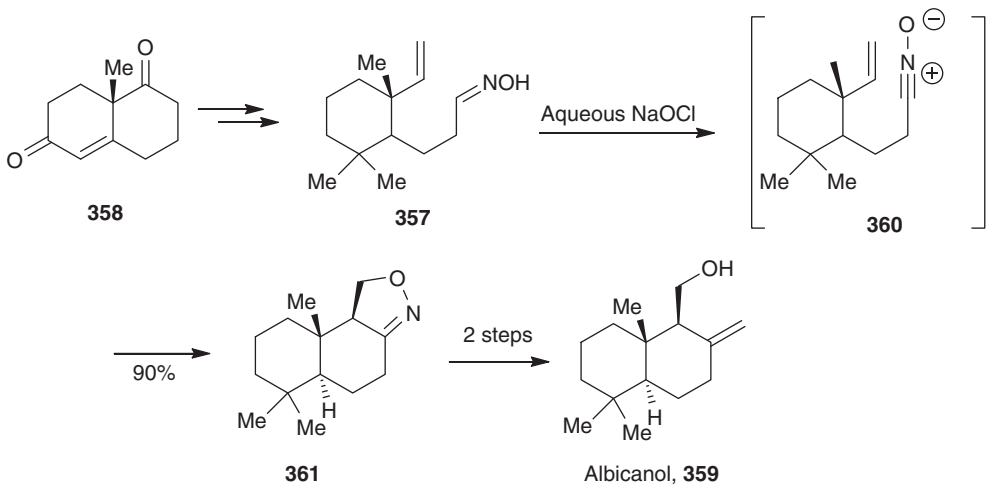
4.21.6 Nitrile Oxides

The chemistry of nitrile oxides is very rich and well-documented.[147] Nitrile oxides are most commonly generated from aldehydes via oxime formation, oxidation to hydroximoyl chlorides using sodium hypochlorite, and subsequent base-mediated dehydrohalogenation.[148] Mukaiyama reaction of primary nitro compounds with isocyanates constitutes another important method of generation of these dipoles.[149] Nitrile oxides are generally unstable and undergo facile dimerization reactions; however, a number of sterically hindered nitrile oxides have been isolated. Intramolecular nitrile oxide cycloaddition (INOC) reactions with alkenes or alkynes afford fused isoxazolines or isoxazoles that are well-known precursors of β-amino alcohols and β-hydroxy ketones (Scheme 103).[150]



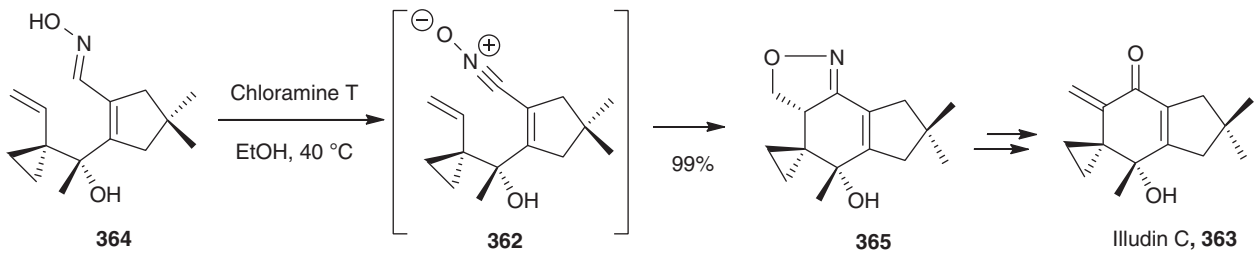
Scheme 103

The efficiency and stereoselectivity of INOC reactions have made them a useful tool for the construction of carbocyclic frameworks of many natural terpenoids. For example, the oxime **357** derived from (+)-Wieland–Miescher ketone **358** was employed in an asymmetric synthesis of drimane sesquiterpene, albicanol **359**. Nitrile oxide **360**, generated from **357**, underwent INOC reaction with the tethered alkene to furnish the cycloadduct **361** in excellent yield (Scheme 104).[151]



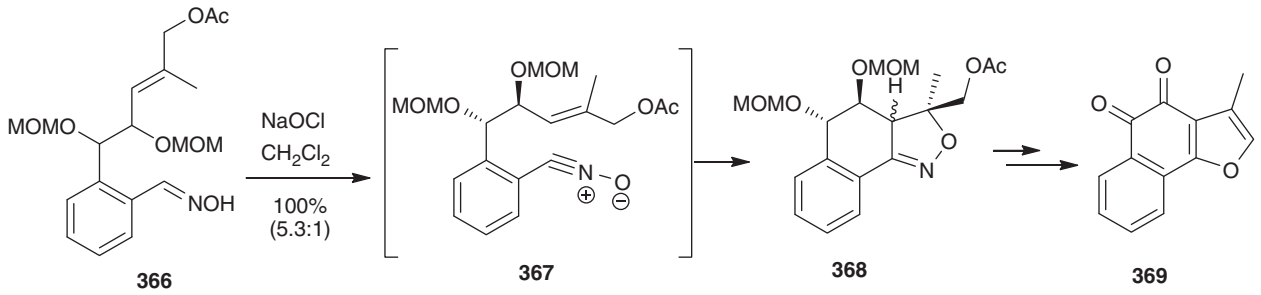
Scheme 104

A remarkable IDC reaction of the nitrile oxide **362** carrying a cyclopropane ring and an allylic alcohol moiety was employed in the total synthesis of the sesquiterpene (±)-illudin C **363**. The oxime **364** was subjected to oxidation with chloramine T to generate the nitrile oxide **362**, which underwent smooth INOC reaction to produce the cycloadduct **365** in quantitative yield as a single stereoisomer (Scheme 105).[152]



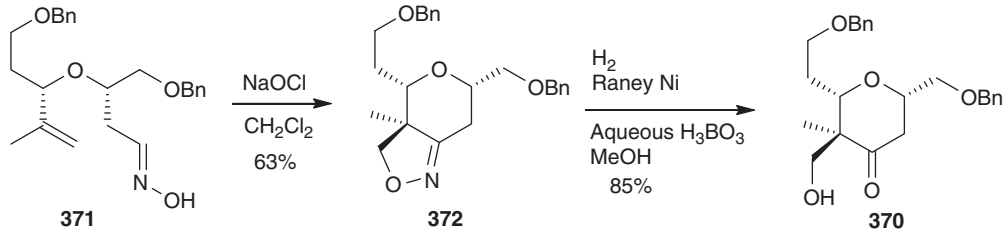
Scheme 105

The oxime **366**, incorporating three protected hydroxyl moieties, was oxidized with NaOCl to generate the corresponding nitrile oxide **367** without affecting the alcohol masking groups. INOC reaction of the nitrile oxide with the tethered disubstituted *cis*-alkene afforded a separable mixture (5.3:1) of diastereomers of the cycloadduct **368**. The latter was converted into the furan-fused *ortho*-quinone **369** which represents an integral structural unit of the family of diterpenes known as tanshinones (Scheme 106).[153]



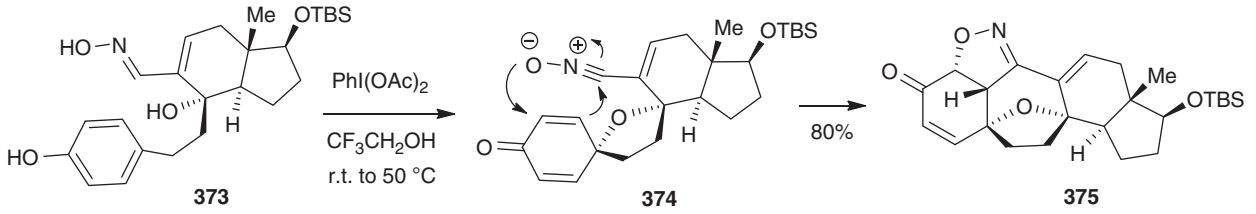
Scheme 106

Asymmetric synthesis of a tetrahydropyranone derivative **370** incorporating a quaternary center was achieved by means of an INOC reaction. Nitrile oxide generated from the chiral oxime **371** underwent smooth cycloaddition with the tethered alkene to afford the cycloadduct **372** as a single stereoisomer. The latter was reduced to obtain the *β*-hydroxy ketone **370** that was carried forward in the synthesis of the antitumor macrolide, (−)-lasonolide A (Scheme 107).[154]



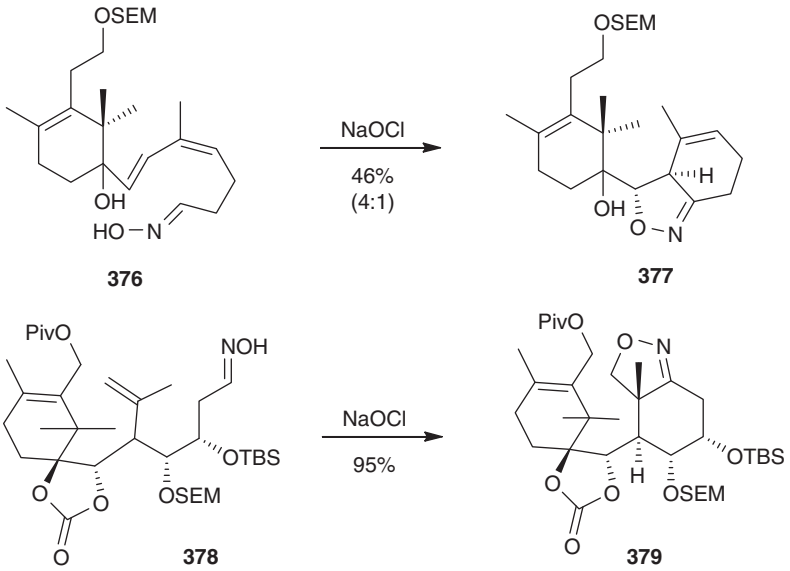
Scheme 107

The primary reason behind the popularity of sodium hypochlorite as the oxidizing agent for the generation of nitrile oxides from aldoximes is its inertness toward alkenes and some other oxidizable functional groups. Although oxidation at multiple sites is problematic, it may be exploited to design cascade reactions involving nitrile oxides. In this context, the use of bis(acetoxy) iodobenzene as an oxidant for the conversion of aldoximes to nitrile oxides in tandem with the oxidative dearomatization of a phenol is noteworthy.[155] This hypervalent iodine reagent was employed in an elegantly orchestrated cascade reaction of the aldoxime **373** involving an ether ring formation via oxidative dearomatization, conversion of oxime to the nitrile oxide **374**, and subsequent INOC reaction. The complex pentacycle **375**, embodying the molecular architecture of the cortistatin class of natural products, was formed in 80% yield as a single diastereomer (Scheme 108).[156] Incidentally, an early-stage intermolecular nitrone–alkene cycloaddition was a key transformation in the synthesis of the cycloaddition substrate **373**.



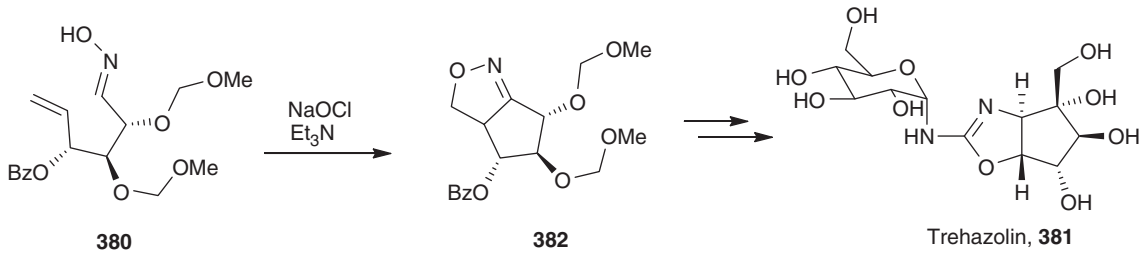
Scheme 108

The synthesis of the C-ring of taxol by means of an INOC reaction is the subject matter of two independent reports. The first of these studies, describes the generation of the dipole by NaOCl oxidation of the oxime **376**, leading to the formation of a separable mixture of diastereomeric cycloadducts **377**. It is noteworthy that the dipolarophile was part of a 1,3-diene system and an adjacent hydroxyl group was unprotected during the oxidation–INOC reaction sequence.[157] The second and a more recent report featured an INOC reaction of the advanced synthetic intermediate **378** to afford the highly oxygenated cycloadduct **379** (Scheme 109).[158]



Scheme 109

An alkenyl oxime **380** in which both the functional groups are connected by means of a chiral carbohydrate-derived backbone was employed in a key INOC reaction in the total synthesis of the antibiotic pseudosacccharide, trehazolin **381**. Treatment of the oxime with NaOCl and triethylamine afforded the cycloadduct **382** which was further manipulated to complete the synthesis of trehazolin **381** (Scheme 110).[159]



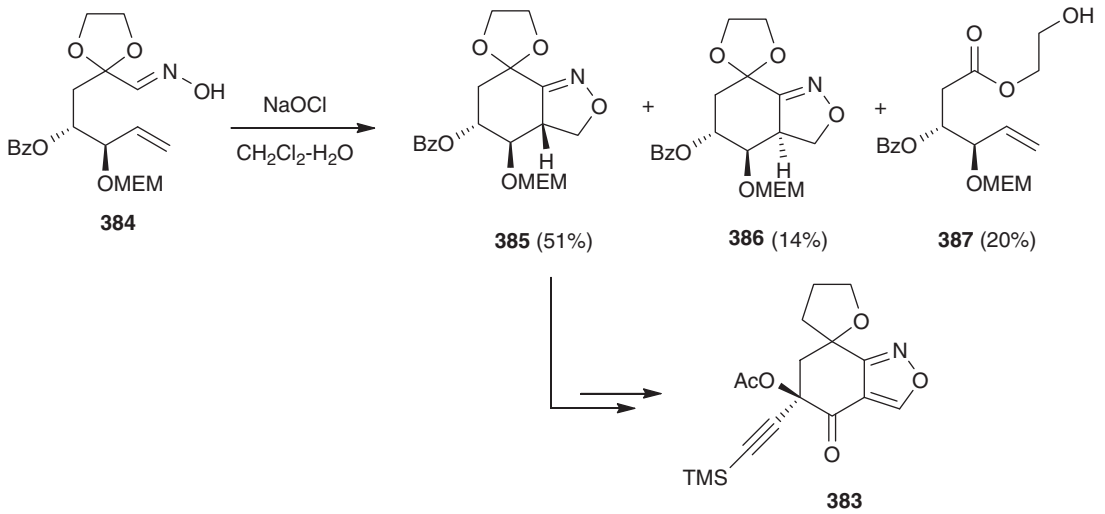
Scheme 110

An important keto-isoxazole building block **383** used in the total synthesis of the enediyne antibiotic calicheamycin was put together via the INOC reaction of the nitrile oxide derived from the aldoxime **384**. The cycloaddition afforded a mixture of diastereomeric products **385** and **386** in a 4:1 ratio (65% combined yield) along with a small amount of the ester **387**. The isoxazole **383**, obtained in a few operations from the desired, major isomer **385**, was then employed for the synthesis of calicheamycin (Scheme 111).[160]

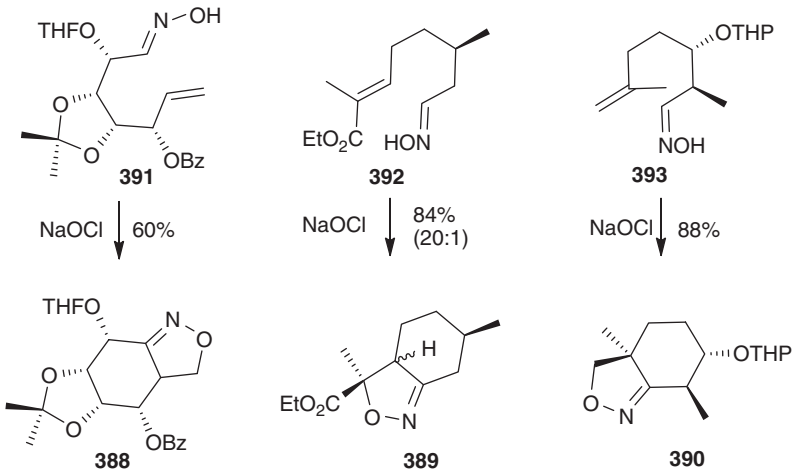
The chiral isoxazolines **388**, **389**, and **390** produced by the oxidation–INOC reaction sequence of the oximes **391**, **392**, and **393**, respectively, are a few examples of functionalized cycloadducts that have been employed as advanced intermediates in the targeted syntheses of various products (Scheme 113). Although the acetonide cycloadduct **388** was used in the synthesis of the carbosugars, Gabosines C and E,[161] the ester **389** served as an intermediate for the preparation of the butenolides, (−)-mintlactone and (+)-isomintlactone.[162] Cassiol, the aglycon of the antiulcerogenic natural product cassioside, was the final target of the synthetic effort involving the cycloadduct **390** (Scheme 112).[163]

Baylis–Hillman adducts, owing to their multifunctional nature, constitute versatile building blocks for the synthesis of substrates for IDC reactions (*vide supra*). INOC reactions are no exceptions, as illustrated by the *N*-chlorosuccinimide (NCS)-mediated oxidation of the oximes **394**, that are derived from Baylis–Hillman adducts. The INOC reactions afforded a library of angularly substituted tricyclic chromenoisoxazolines **395**, containing two adjacent stereocenters, one of them being an all-carbon quaternary one, in high yields and stereoselectivity (Scheme 113).[164]

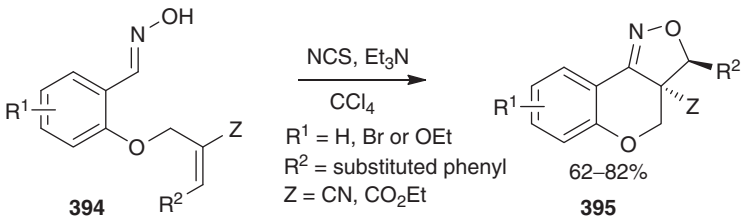
A library of β-carboline-based polycyclic natural product like molecules **396** were synthesized by subjecting oximes **397** derived from 1-formyl-9H-β-carbolines to oxidative conditions. The nitrile oxides thus generated underwent rather slow (3 days) cycloaddition reactions with pendant alkenes to afford the polycyclic products (Scheme 114). Related heterocycles such as isoxazoles and triazoles were also synthesized from corresponding oxime-alkynes and azido-alkynes, respectively.[165]



Scheme 111



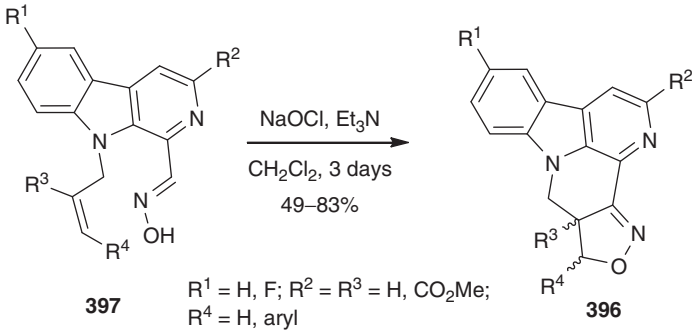
Scheme 112



Scheme 113

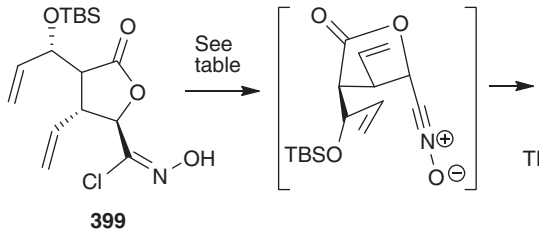
A study directed toward the total synthesis of the natural product branimycin revealed interesting features of temperature dependence of the efficiency of intramolecular nitrile oxide–alkene cycloaddition reactions. It was observed that the yield of the cycloadduct **398** from the hydroximoyl chloride **399** steadily increased with temperature (Scheme 115). It is presumable that, due to strain, the activation enthalpy for intramolecular cycloaddition is higher than the competing intermolecular process. An increase in temperature, therefore, accelerates the former reaction *vis-a-vis* dimerization resulting in selective formation of the intramolecular cycloadduct.[166]

The outcome of intramolecu1ar 1,3-dipolar cycloadditions of nitrile oxides **400** prepared from 3-*O*-alkenyl-1,2-*O*-isopropylidene-*α*-D-pentodialdofuranoses **401** is dictated by the length of the alkenyl chain. Tetrahydropyrans **402a**[167] and oxepanes



397 R^1 = H, F; R^2 = R^3 = H, CO_2Me; R^4 = H, aryl **396**

Scheme 114

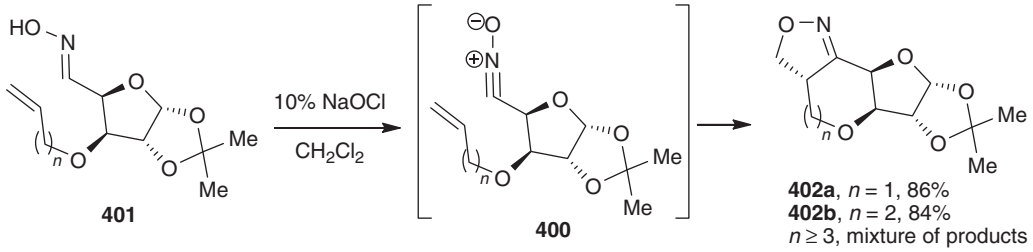


399 **398**

Temperature	Yield (%)
0	53
22	63
40	70
60	74
80	79

Scheme 115

402b were produced from *O*-allyl and *O*-homoallyl derivatives, respectively, whereas 3-*O*-pentenyl nitrile oxide **400** ($n=3$) produced a mixture of *exo*- and *endo* adducts. Higher tether lengths also led to the formation of mixtures of cycloadducts (Scheme 116).[168]

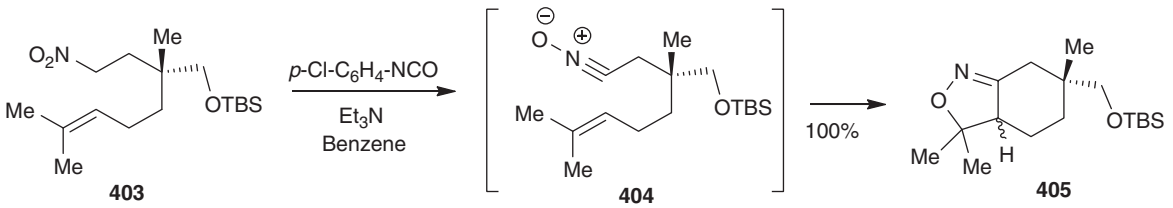


401 **400**

402a, n = 1, 86%
402b, n = 2, 84%
$n \geq 3$, mixture of products

Scheme 116

Dehydration of primary nitro compounds constitutes a convenient and popular method of generation of nitrile oxides. For example, the geraniol-derived nitro compound **403**, was converted into the transient nitrile oxide **404**, which underwent a facile INOC reaction to afford the cycloadduct **405** in quantitative yield (Scheme 117). Although a mixture of diastereomeric cycloadducts were formed in the INOC reaction, both of them converged into a single product at a later stage of the synthesis the target of which was a fragrant sesquiterpene, nanaimoal.[169]

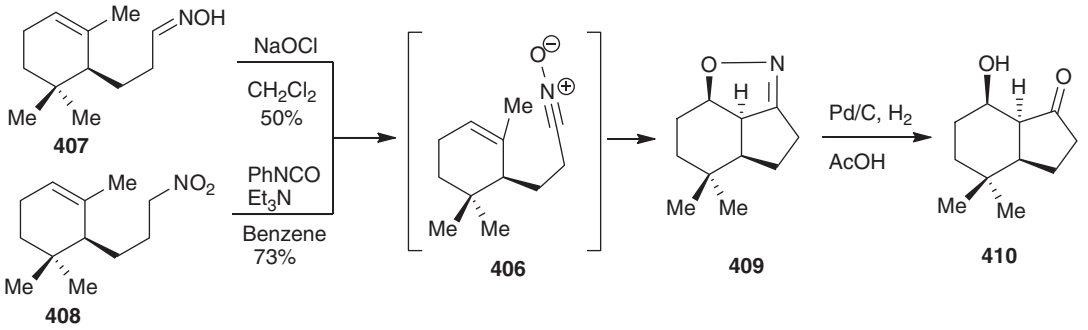


403 **404** **405**

Scheme 117

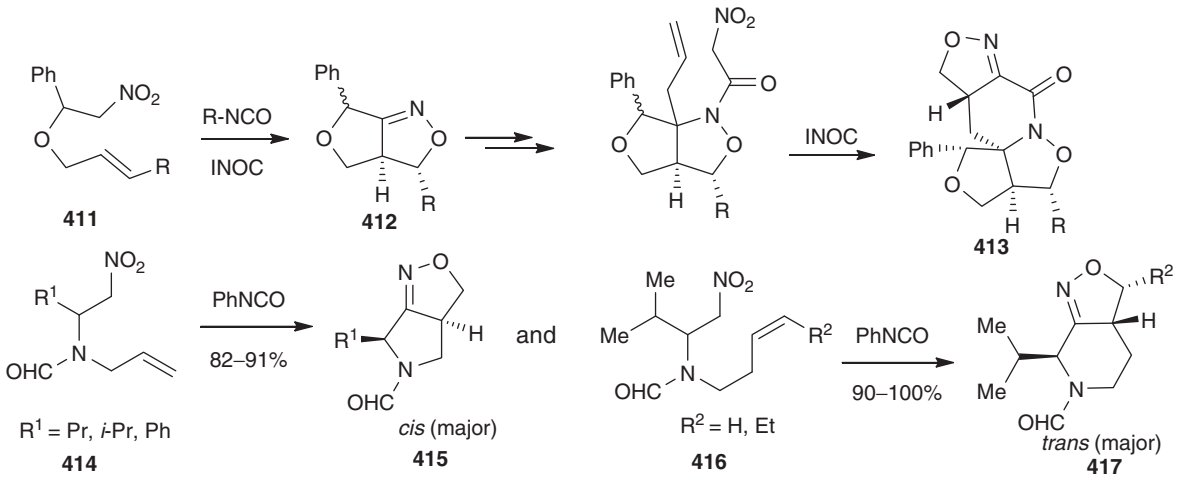
Nitrile oxide **406**, generated independently from the oxime **407** and nitro compound **408**, underwent stereoselective INOC reaction to afford the cycloadduct **409** in 50% and 73% yields, respectively. Reductive cleavage of the isoxazoline ring in **409**

furnished the hydroxy ketone **410** which was then employed in the synthesis of the tricyclic framework of the insect antifeedant, 12-hydroxyazadiradione (Scheme 118).[170]



Scheme 118

Conjugate addition of suitable nucleophiles to nitroalkenes affords functionalized primary nitro compounds that serve as precursors for nitrile oxides. The easy access to nitroalkenes via Henry reaction combined with the facile generation of nitrile oxides help in creating substantial molecular complexity in a few steps from simple starting materials as illustrated by the examples in Schemes 119–120. Allylic ethers **411**, prepared by conjugate addition of nitroalkenes, were subjected to iterative INOC reactions to afford bicyclic and tetracyclic frameworks such as **412**–**413**.[171] Similarly, *N*-formyl-*β*-nitroamides **414**, resulting from a hetero-Michael addition of allylic formamides to nitroalkenes, underwent stereoselective INOC reaction to afford *cis*-pyrroloisoxazoles **415**. Interestingly, related homoallyamides **416** afforded the *trans*-piperidinoisoxazoles **417** as the major product (Scheme 119).[172] The stereochemical outcome is the result of the dipole assuming a favorable conformation in which the *α*-substituent occupies an axial position to avoid gauche interaction with the *N*-formyl group.

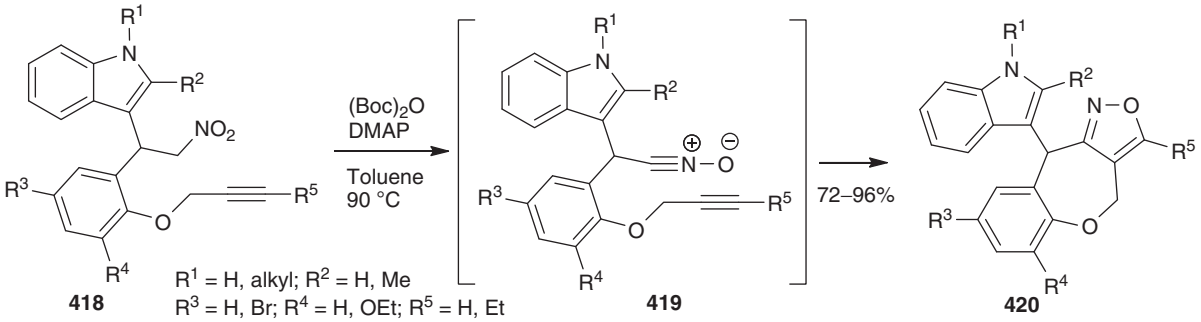


Scheme 119

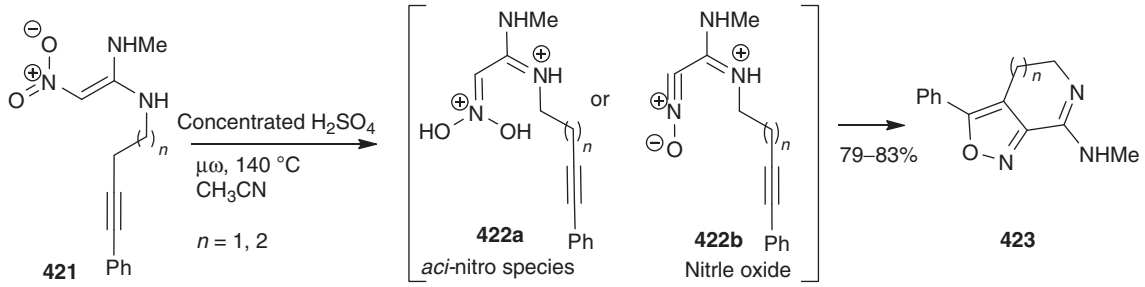
In a somewhat complementary approach, *β*-nitrostyrenes endowed with a tethered dipolarophile were subjected to Michael addition with indoles and the primary nitro compounds **418** thus obtained were then converted into the corresponding nitrile oxides **419**. The dehydration was carried out by di-*tert*-butyl dicarbonate in toluene and excellent yields of isoxazolobenzoxepanes **420** were obtained (Scheme 120).[173]

Treatment of 1,1,-diethenamines **421** with acid generated a reactive 1,3-dipole **422** which underwent intramolecular cycloaddition with the alkyne unit to afford bicyclic isoxazoles **423** (Scheme 121). It is equally plausible that the 1,3-dipole involved is a nitrile oxide **422a** or an *aci*-nitro species **422b**. Microwave irradiation enhances the rate of the annulations significantly.[174]

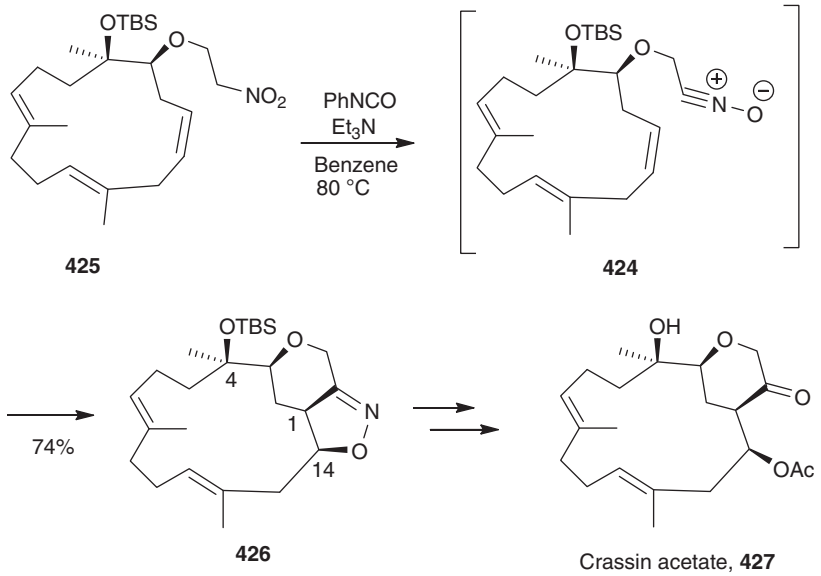
Nitrile oxide **424** generated from the nitro ether **425** annulated the *cis*-alkene present in a macrocyclic framework to afford the tricyclic isoxazole **426**. This INOC reaction installed two rings and two stereocenters at adjacent carbons on the macrocycle. The antibiotic lactone, crassin acetate **427** was accessed from the cycloadduct **426** in a few steps (Scheme 122).[175]



Scheme 120



Scheme 121



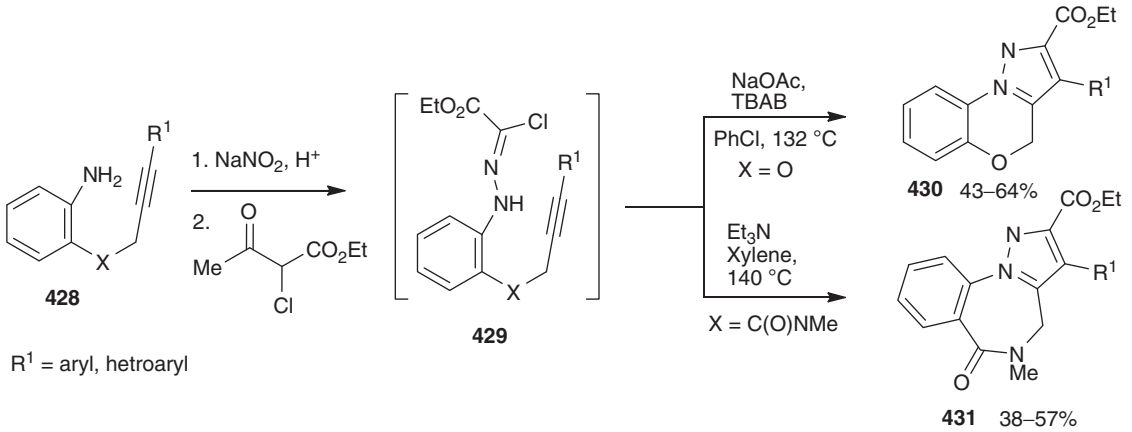
Scheme 122

4.21.7 Nitrile Imines

Nitrile imines are transient dipoles commonly generated via the base-mediated dehydrohalogenation of hydrazonoyl chlorides. Dipolar cycloaddition reactions of these dipoles with alkenes or alkynes afford dihydropyrazoles and pyrazoles, respectively. A few selected examples of IDC reactions of nitrile imines are described in this section.

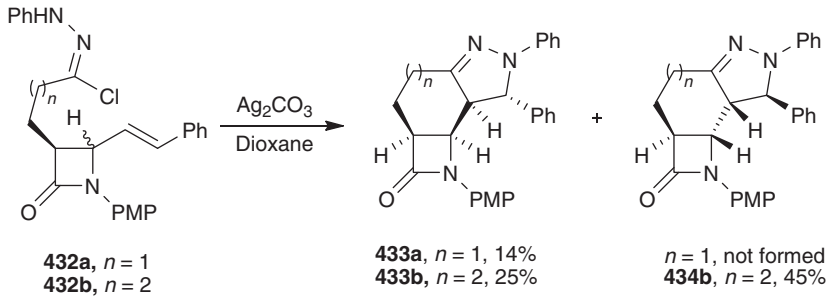
Japp–Klingemann reaction of the diazo compounds generated from substituted anilines **428** afforded hydrazonoyl chlorides **429** that served as precursors of corresponding nitrile imines. Pyrazolobenzoxazines **430** and pyrazolobenzodiazepinones **431**

were obtained in moderate yields when crude samples of the alkyne-tethered hydrazonoyl chlorides **429** were heated in the presence of the base (Scheme 123).[176]



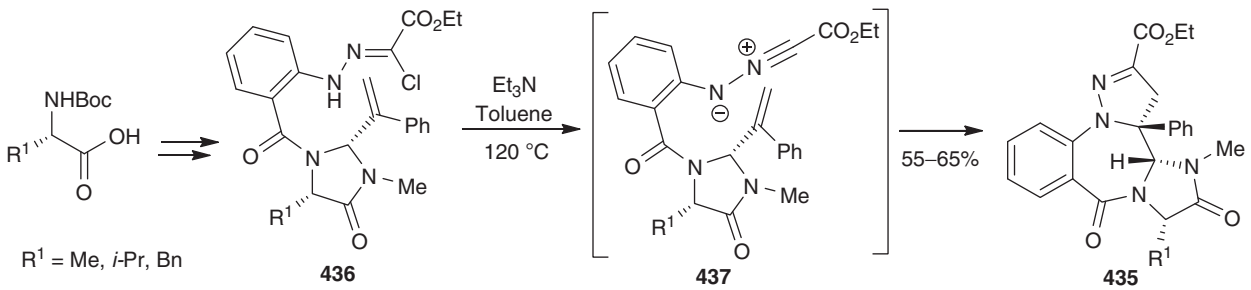
Scheme 123

Nitrile imines and alkenyl dipolarophiles anchored onto adjacent carbon atoms of a β-lactam ring underwent stereoselective dipolar cycloaddition reactions to afford tricyclic β-lactam derivatives. The nitrile imines were generated by treating the hydrazonoyl chlorides **432a,b** with twofold excess of silver carbonate. Interestingly, the β-lactam derivatives **432a,b** were used as a mixture of *cis* and *trans* isomers. Only the *cis* isomer underwent cycloaddition when the dipole and dipolarophile were separated by six carbons to afford the cyclohexane-fused adduct **433a**. However, when the tether was lengthened by one carbon ($n=2$), both the *cis* and *trans* isomers underwent the cycloaddition reaction retaining the diastereomeric ratio in the process. Thus, a mixture of cycloheptane-fused *cis*- and *trans*-substituted β-lactams **433b** and **434b** were obtained from **432b** (Scheme 124).[177]



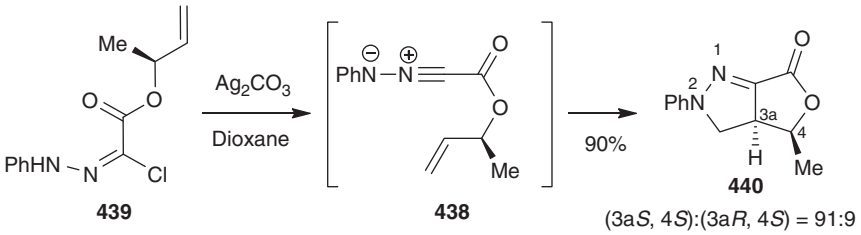
Scheme 124

A new class of tetracyclic imidazo[2,1-c]pyrazolo[1,5-a][s1,4]benzodiazepine-5,8-diones **435** was prepared from chiral amino acids. Base treatment of the amino acid-derived hydrazonyl chlorides **436** generated the nitrile imines **437** which underwent IDC reaction with the styrenic double bonds in a completely regio- and stereoselective fashion to afford optically pure cycloadducts **435** as single diastereomers (Scheme 125).[178]



Scheme 125

Nitrile imine **438** generated from the chiral hydrazonoyl chloride **439** underwent smooth IDC reaction with the alkene appendage to afford the cycloadduct **440** in excellent yield and diastereoselectivity. The effect of the asymmetric center in **439** at the α-position of the nitrile imine on the newly formed chiral carbon was rationalized by means of MP2 calculations (Scheme 126).[179]

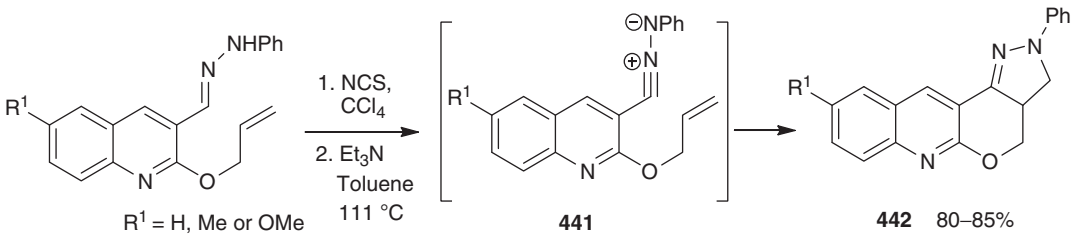


439 **438** **440**

(3a*S*, 4*S*):(3a*R*, 4*S*) = 91:9

Scheme 126

The IDC of quinoline-derived nitrile imines **441** afforded dihydrazole-fused pyrano-quinolines **442** in excellent yields (Scheme 127).[180]

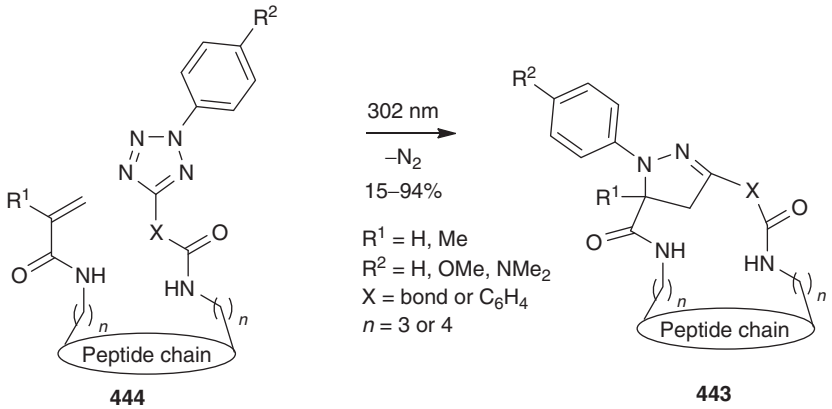


R^1 = H, Me or OMe

441 **442** 80–85%

Scheme 127

Intramolecular nitrile–imine alkene cycloaddition has been successfully employed for macrocyclic cross-linking of peptide side chains (peptide stapling) to afford pyrazoline peptides **443** with unique fluorescence properties. Interestingly, the nitrile imines were generated by photoinduced extrusion of nitrogen from peptide-derived tetrazoles **444** (Scheme 128). The highest yield of the stapled product (94%) was obtained for a linear peptide carrying a *N*-(4-dimethylamino)phenyl tetrazole moiety as the dipole precursor and a methacrylamide unit as dipolarophile. The stapling reaction tolerated polar side chains and proceeded in protic solvents such as ethanol, isopropanol, and water.[181]



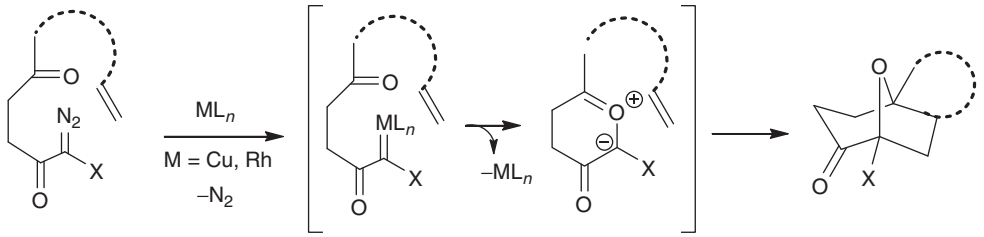
444 **443**

Scheme 128

4.21.8 Carbonyl Ylides

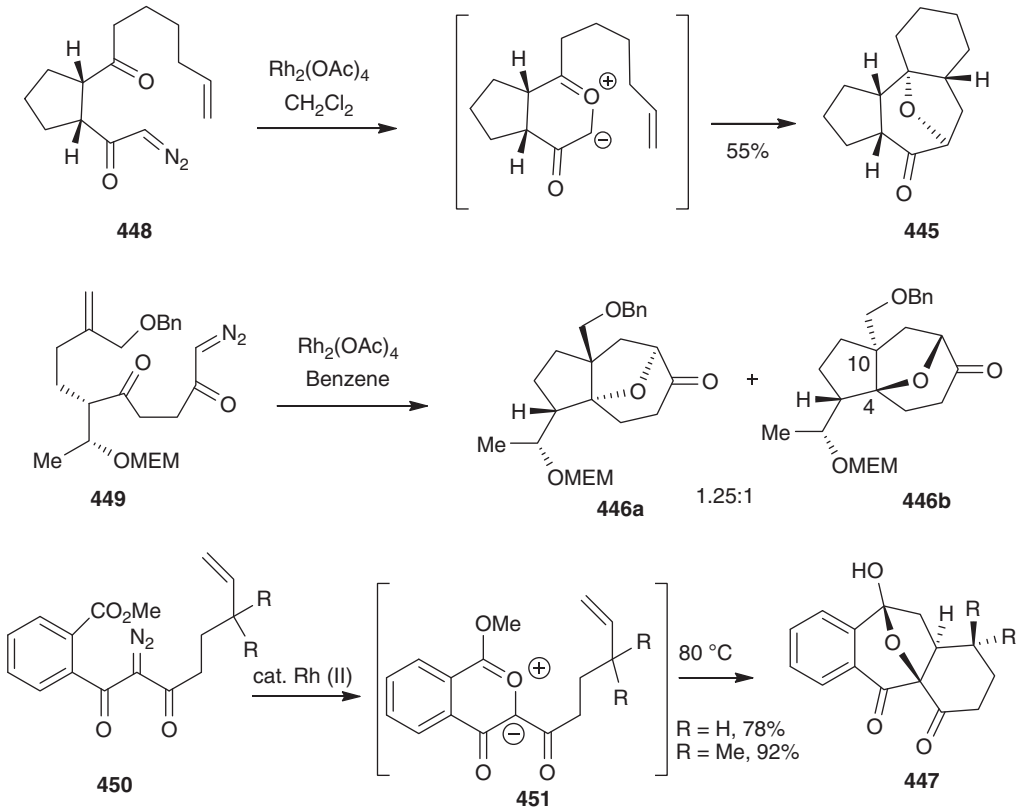
IDC reactions of carbonyl ylides constitute a very powerful tool for the quick generation of molecular complexity from relatively simple precursors.[182] Carbonyl ylides are transient species that can be generated *in situ* by thermolysis or photolysis of oxiranes[183]

and 1,3,4-oxazolidines.[184] The most widely employed method for the generation of carbonyl ylides, however, is the rhodium-catalyzed decomposition of diazo compounds in the presence of a carbonyl compound.[185] Often, α-diazoketones containing another carbonyl unit as part of the same molecule are employed, resulting in the formation of cyclic carbonyl ylides. These reactive 1,3-dipoles are not isolated and they undergo facile IDC reactions with tethered dipolarophiles (Scheme 129). Reactions of the mesionic dipoles, isomünchnones, that formally belong to the broad class of carbonyl ylides are also included in the following discussion for convenience.[186]



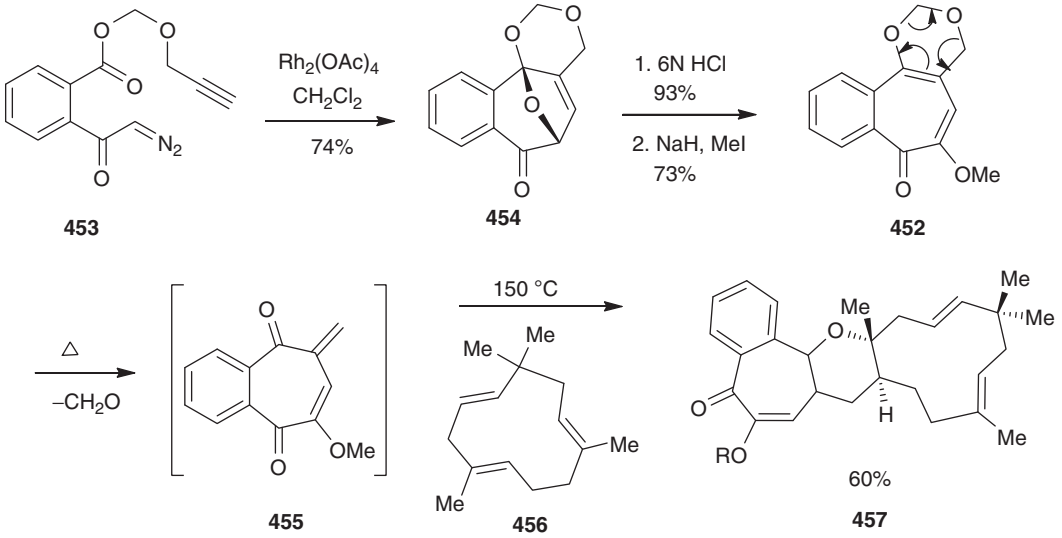
Scheme 129

The first report of an IDC reaction of a carbonyl ylide appeared in 1980.[187] Since then, a variety of intramolecular carbonyl ylide alkene cycloaddition (ICAC) reactions have been developed and employed for natural product synthesis, most notably by Padwa and coworkers.[188] A majority of ICAC reactions involve the generation and interception of cyclic carbonyl ylides. Since oxo-bridged carbocycles can be conveniently accessed via ICAC reactions, they have found numerous applications in terpenoid synthesis. For example, the oxo-bridged tricyclic ring system **445** of the trigliane diterpene, phorbol,[189] the bicyclic skeleton **446a**,**b** of pseudolaric acids[190], and the bridged dodecanedione substructure **447** of the icetexane diterpene, komaroviquinone[191] were synthesized using ICAC reactions of the diazo ketones **448**–**450** (Scheme 130). These cycloaddition reactions generally proceed at room temperature except in the case of the carbonyl ylide **451**. The latter underwent an internal ring closure at room temperature to form an epoxide. At a higher temperature (80 °C), however, both the diazo compound **450** and the isolated epoxide, afforded the desired tetracyclic product **447**.[192]



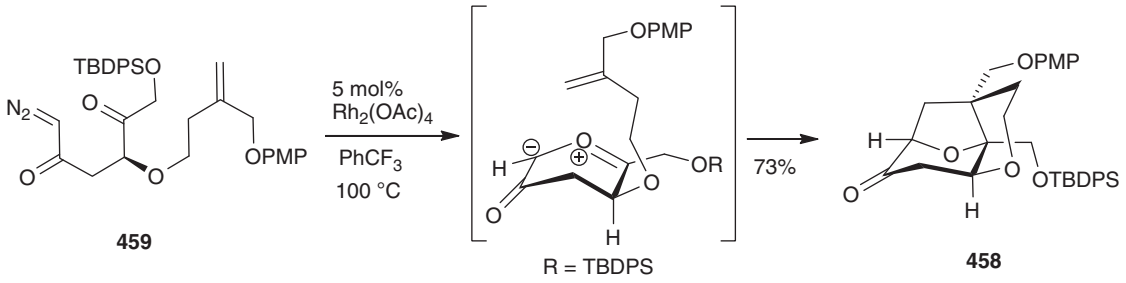
Scheme 130

The tropolone moiety **452** found in the fungal metabolites pycnidione and epolone B was synthesized via an intramolecular carbonyl ylide–alkyne cycloaddition of the diazoketone **453**. The cycloadduct **454**, when exposed to acid, underwent cleavage of the oxa-bridge to afford the benzotropolone derivative **452**. The latter served as the precursor to the reactive quinone methide **455** which on interception by humulene **456** afforded an analog of the natural product **457** (Scheme 131).[193]



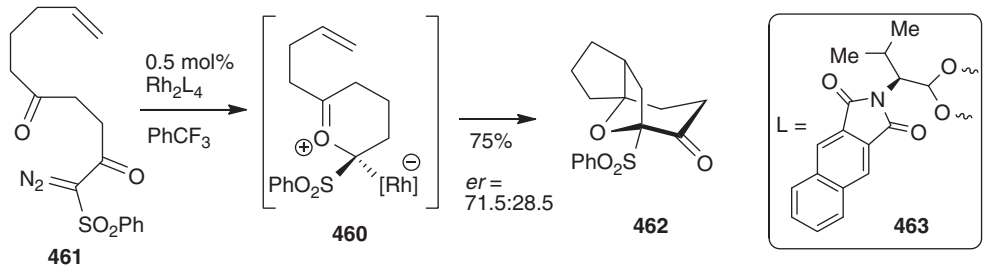
Scheme 131

The unique trioxatetracyclic ring system **458** present in the natural products polygalolides A and B was assembled by a carbonyl ylide-generation–IDC sequence. The diazo compound **459** on treatment with rhodium acetate generated the tetracyclic compound **458** in 73% yield as a single isomer (Scheme 132). The latter was further advanced to the natural products in a few steps.[194]



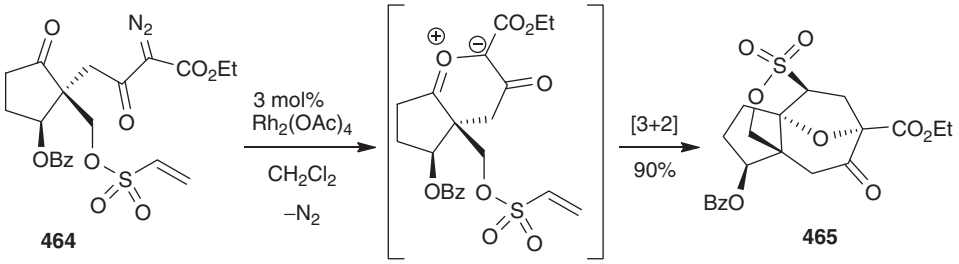
Scheme 132

Chiral ligands can be employed in combination with rhodium catalysts to afford enantiomerically enriched cycloadducts from ICAC reactions. Carbonyl ylides **460** generated from unsaturated *α*-diazo-*β*,*ε*-diketo sulfones **461** in the presence of chiral rhodium catalysts underwent smooth cycloaddition with tethered terminal alkenes to afford the tricyclic adduct **462** (Scheme 133). Among the few chiral ligands screened, the valine-derived naphthalene dicarboximide **463** afforded the best results.[195]



Scheme 133

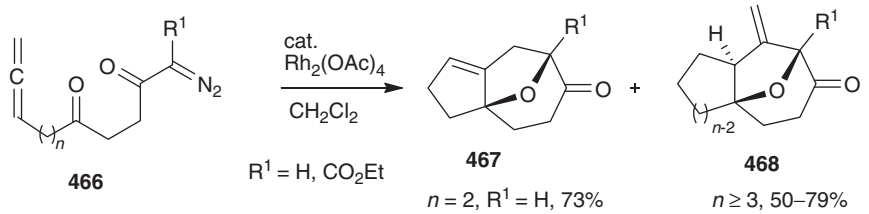
As evident from the examples described before, the alkene and alkyne dipolarophiles need not be activated in ICAC reactions. Electron-withdrawing substituents on the dipolarophiles, however, have been shown to improve the yield and stereoselectivity of the cycloaddition reaction. This effect is demonstrated in the case of vinyl sulfonate **464**, which underwent smooth Rh-catalyzed ICAC reaction at room temperature to furnish polycyclic sultone **465** in excellent yield and diastereoselectivity (Scheme 134).[196]



464 **465**

Scheme 134

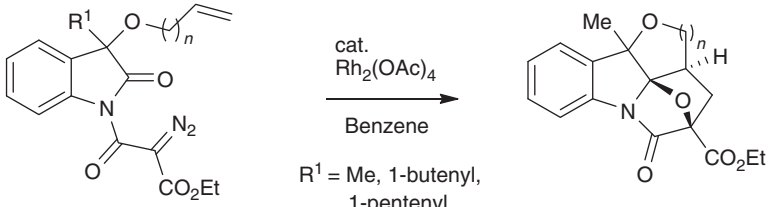
Allenes also function as reactive dipolarophiles in IDC reactions of carbonyl ylides. This is illustrated with a series of allenyl diazo compounds **466** which furnished oxatricyclic adducts **467–468** as single diastereomers (Scheme 135). The internal double bond of the allenes reacted except when the tether was prohibitively short.[197]



466 R^1 = H, CO_2Et **467** n = 2, R^1 = H, 73% **468** $n \geq 3$, 50–79%

Scheme 135

The IDC reaction of carbonyl ylides generated from α-diazo dihydroindolinones **469** is a facile method for quickly assembling complex azapolycyclic ring systems. Both alkenes and tethered alkenyl ethers function as dipolarophiles by readily undergoing the intramolecular cycloaddition to afford 5-, 6-, and 7-membered rings fused to the dihydroindolinone framework **470** in good yields (Scheme 136).[198]



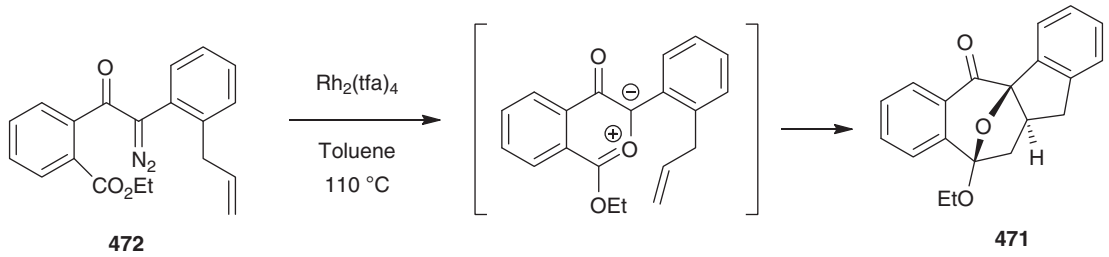
469 n = 1, 2, 3 R^1 = Me, 1-butenyl, 1-pentenyl **470** 55–82%

Scheme 136

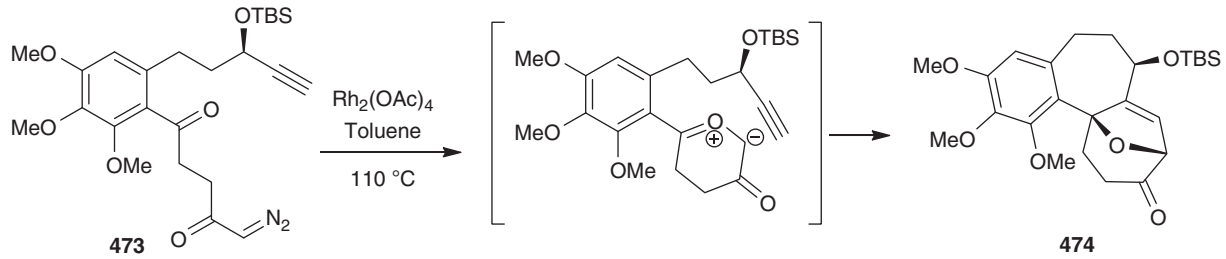
An oxabicyclo[3.2.1]octane system **471**, resembling the core structure of the alkaloid (±)-ribasine, was synthesized from *o*-allylphenyl-substituted α-diazoketone **472**. A byproduct resulting from an IDC of the diazo group was also observed in this case (Scheme 137).[199]

An Rh-catalyzed IDC reaction of the homochiral α-diazoketone **473** with the tethered alkyne was a key transformation in an asymmetric total synthesis of (−)-colchicine. The cycloaddition was carried out in toluene at 110 °C to afford the oxatetracyclic compound **474** with nearly complete diastereoselectivity. The cycloadduct was then carried forward in the synthesis to furnish the alkaloids (−)-colchicine and (−)-isocolchicine (Scheme 138).[200]

A number of examples of carbonyl ylide cycloadditions with indolyl systems are known. This propensity of the indole π-bond to function as a dipolarophile has been exploited in the synthesis of various indole alkaloids. A one-pot carbonyl ylide formation and asymmetric IDC to indole nucleus was employed for the assembly of the pentacyclic skeleton **475** of aspidosperma alkaloids. The catalyst, dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(S-TCPTTL)$_4$, furnished the cycloadduct in

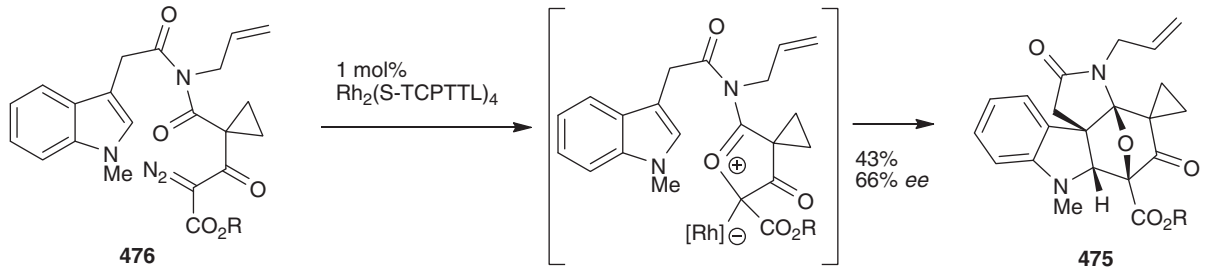


Scheme 137



Scheme 138

moderate yield and enantioselectivity along with an epoxide side product from **476** (Scheme 139). This constitutes the first example of asymmetric induction in an intramolecular cycloaddition of a carbonyl ylide across an indolyl π-bond.[201]



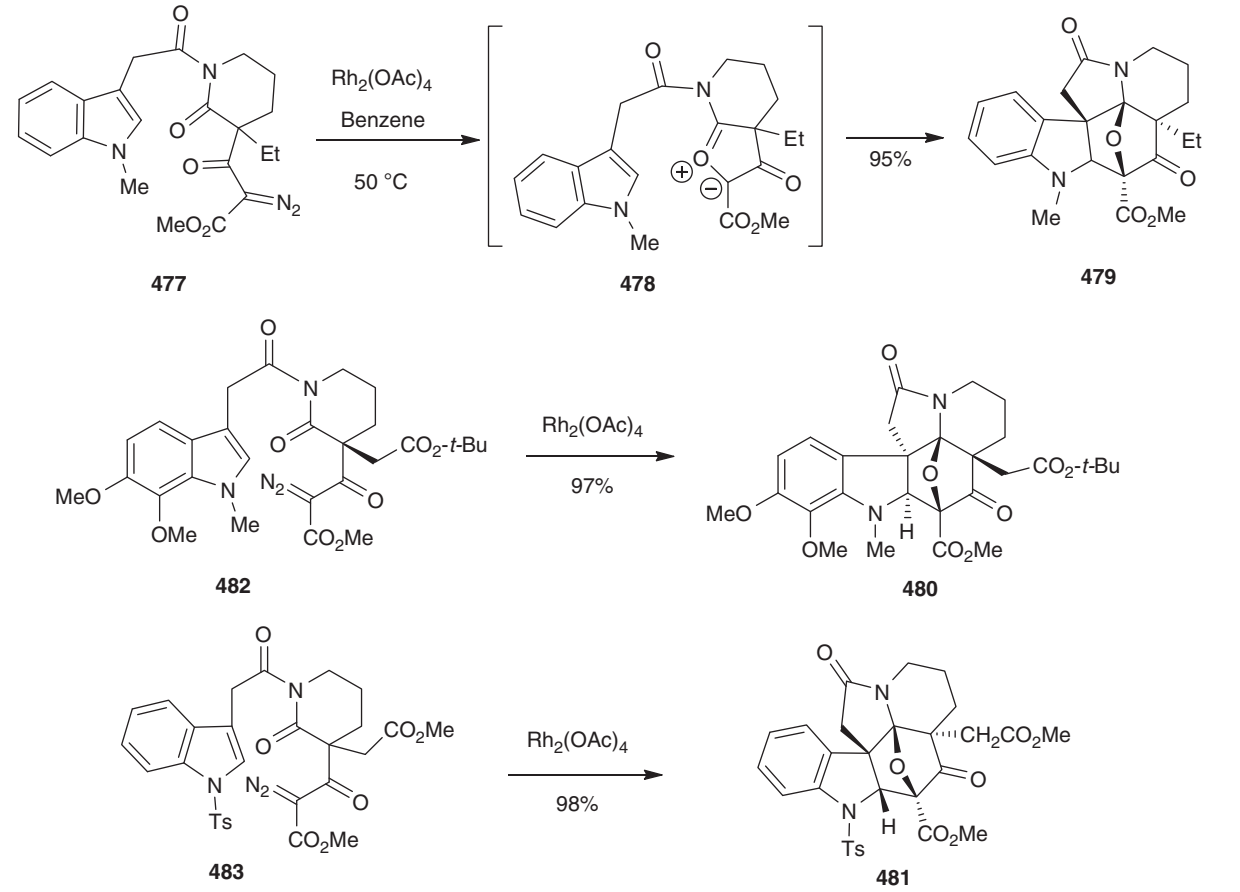
Scheme 139

The IDC of push–pull cyclic carbonyl ylides generated by the action of rhodium(II) on diazoimides have been investigated extensively by Padwa and coworkers. The rhodium carbenoid generated from the diazoimide **477** underwent cyclization to form the carbonyl ylide **478** which spontaneously reacted with the indole double bond to afford the pentacyclic derivative **479**. The cycloaddition installed four new stereocenters with complete diastereoselectivity as a result of a preferred *endo*-addition with regard to the dipole. The pentacyclic skeleton of **479** represents the core structure of the aspidosperma family of alkaloids (Scheme 140).[202] Related polycyclic alkaloid frameworks **480** and **481** were prepared by subjecting respective diazoimides **482** and **483** to similar reaction conditions.[203]

Thermal extrusion of nitrogen from an oxadiazole–alkene cycloadduct is known to generate a push–pull-type cyclic carbonyl ylide.[204] On heating, the alkene-tethered 1,3,4-oxadiazole **484** underwent an intramolecular [4+2] cycloaddition and subsequent cycloreversion with loss of nitrogen to generate the carbonyl ylide **485**. An *endo*-selective IDC reaction of the latter and the indole ring ensued to afford the cycloadduct **486**, which served as an advanced intermediate in a remarkable total synthesis of the alkaloid vindoline **487** (Scheme 141).[205]

Isomünchnones are stable mesionic oxazolium ylides (Figure 1), usually accessed from the rhodium- or copper-catalyzed cyclization of diazoimides. They function as cyclic carbonyl ylides and undergo facile dipolar cycloaddition reactions with various dipolarophiles. A few selected examples of IDC reactions of isomünchnones in targeted syntheses are described in this section.

An intramolecular isomünchnone–alkene cycloaddition reaction was the key step in the total synthesis of the ergot alkaloid, lysergic acid. Rh-catalyzed cyclization of the imidoazide **488** afforded the isomünchnone dipole **489** which underwent a stereoselective IDC reaction with the styrenyl alkene. The cycloadduct **490** was further elaborated to complete the synthesis of lysergic acid (Scheme 142).[206]

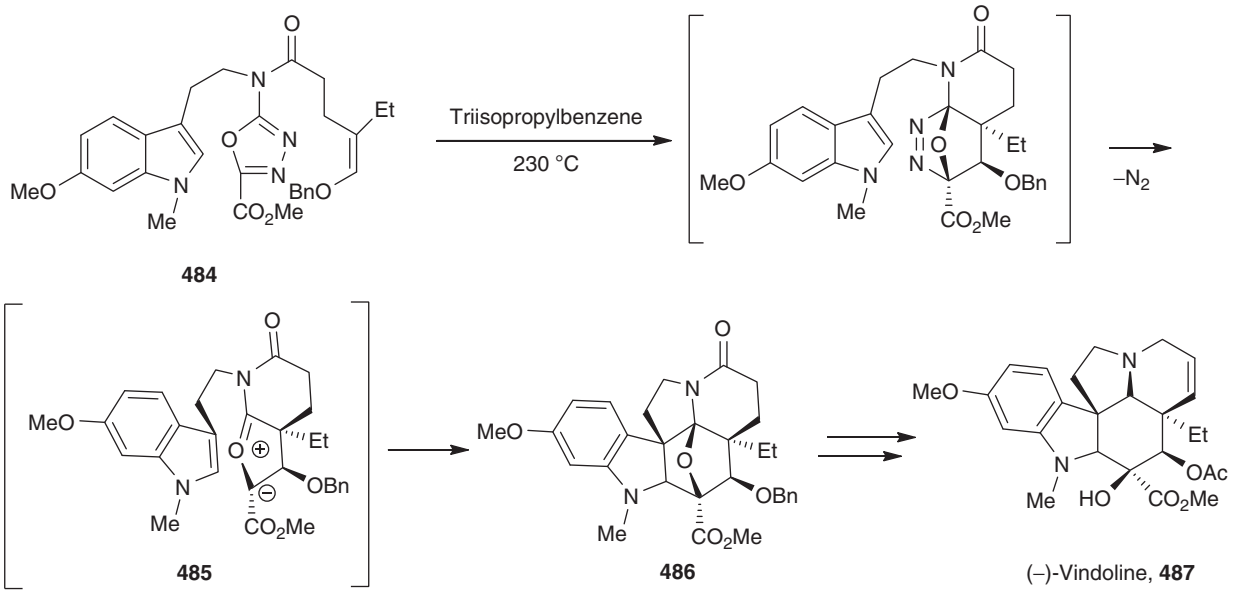


477 **478** **479**

482 **480**

483 **481**

Scheme 140



484

485 **486** (–)-Vindoline, **487**

Scheme 141

IDC of an isomünchnone has served as a key step in a formal total synthesis of the antitumor agent camptothecin **491**. The isomünchnone **492** was generated from the diazo compound **493** on treatment with rhodium acetate in refluxing benzene. A smooth IDC reaction with the sulfonyl alkene unit furnished a 5:1 mixture of diastereomeric cycloadducts (Scheme 143).

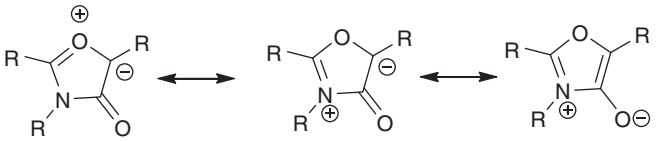
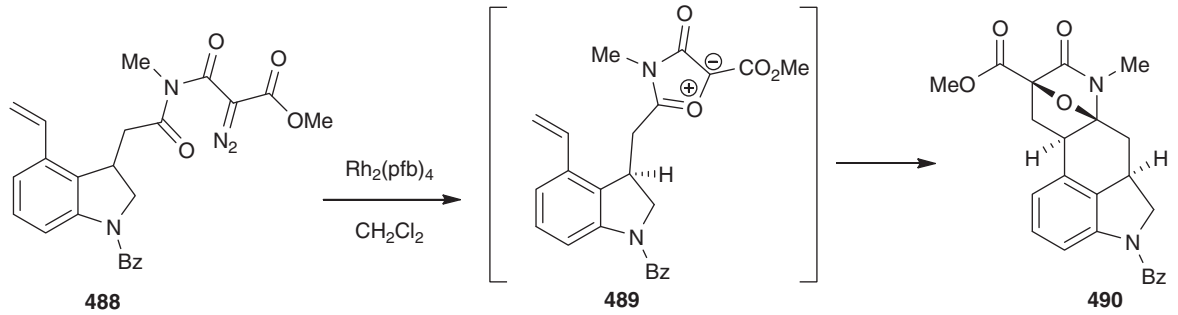
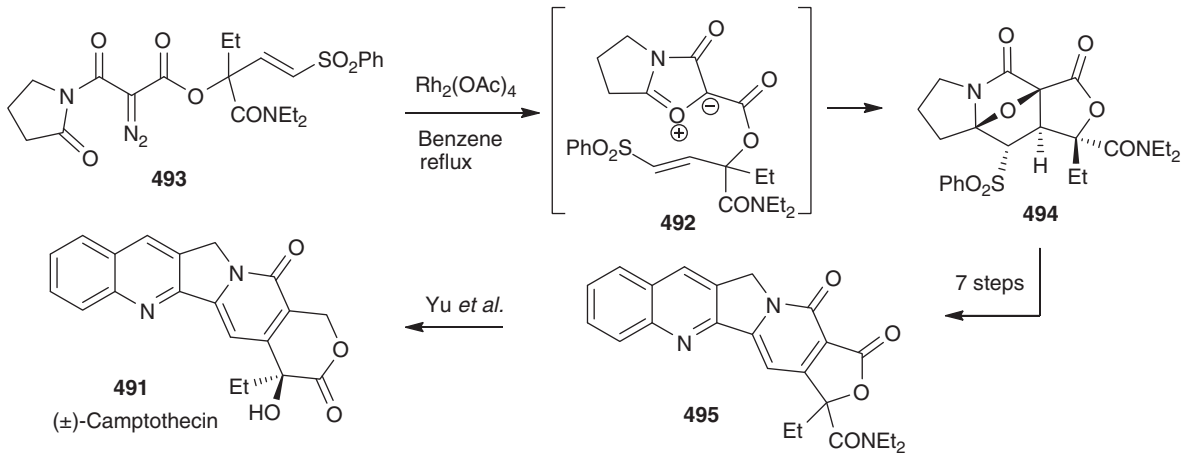


Figure 1 Resonance structures of isomünchnones.



Scheme 142

Conversion of the major cycloadduct **494** to the quinoline **495** in seven steps completed the formal total synthesis of camptothecin.[207]

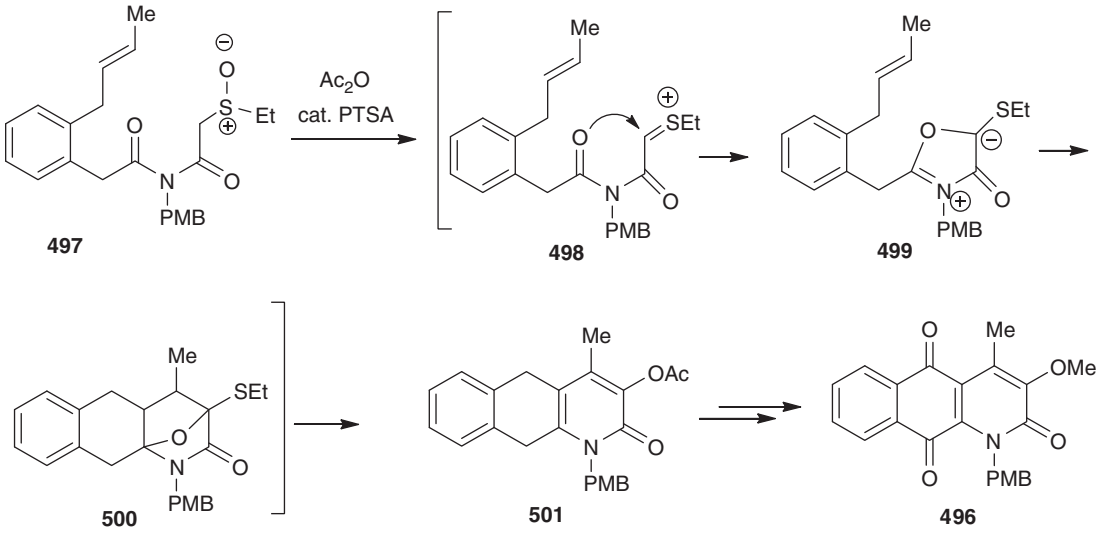


Scheme 143

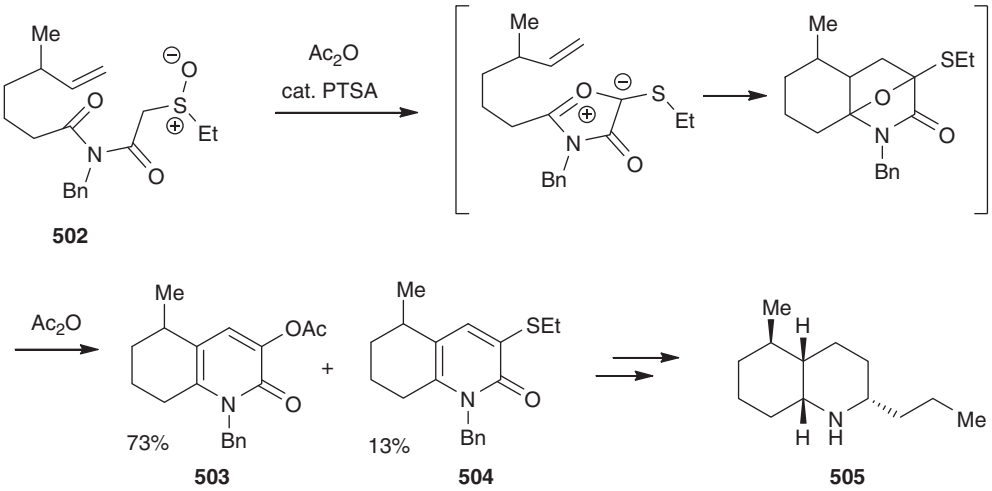
Sulfur-bearing isomünchnone dipoles were generated by the Pummerer reaction of imidosulfoxides. These mesionic dipoles have been employed in the syntheses of a number of alkaloids such as onychnine, dielsiquinone, lupinine, anagyrine, and costaclavine.[208] The synthesis of dielsiquinone **496** is presented in Scheme 145 as a representative example. Pummerer reaction of imidosulfoxide **497** proceeded via internal quenching of the sulfonium intermediate **498** by the imide oxygen. The resulting isomünchnone **499** readily underwent an IDC reaction with the pendant alkene to afford the cycloadduct **500**. In the presence of excess acetic anhydride and catalytic *p*-toluene sulfonic acid, the cycloadduct **500** suffered cleavage of the oxabicyclic ring and the acetoxy pyridone **501** was obtained as the product of the one-pot reaction. The latter was transformed to the natural product **496** in a few steps (Scheme 144).

Formal synthesis of the decahydroquinoline alkaloid, (±)-pumilotoxin C was achieved by employing a tandem Pummerer–isomünchnone dipolar cycloaddition reaction of the imidosulfoxide **502**. A mixture of α-pyridones **503** and **504** were formed in the reaction sequence. Independent conversions of both **503** and **504** to a previously known precursor **505** of pumilotoxin C, constituted a formal synthesis of the natural product (Scheme 145).[209]

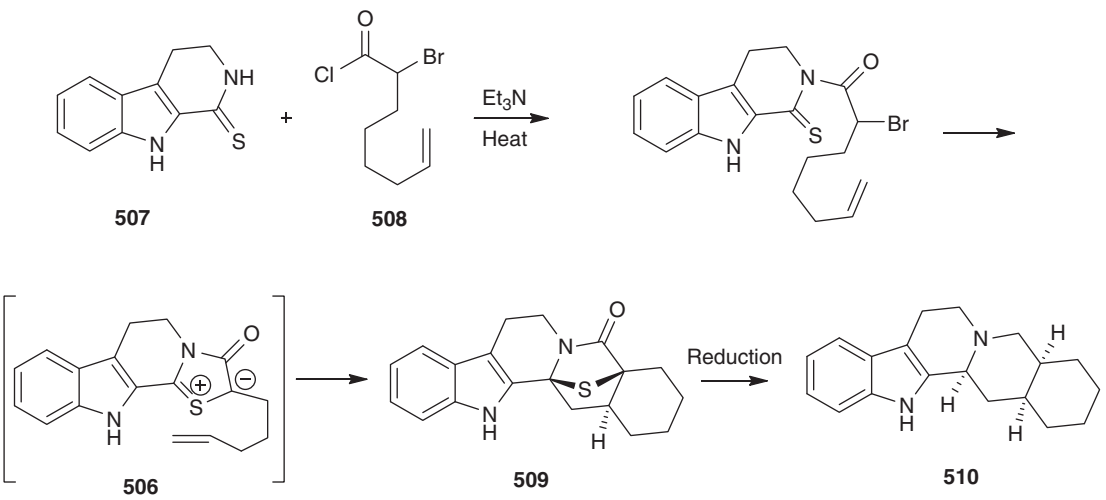
Although not generally considered as carbonyl ylides, thioisomünchnones exhibit reactivity patterns analogous to that of carbonyl ylides. For example, thioisomünchnone **506** was generated by the reaction of thiocarboline **507** and the α-bromo acid chloride **508**. A facile IDC reaction with the terminal alkene ensued to deliver the cycloadduct **509** and the latter was employed in the total synthesis of the alkaloid (±)-alloyohimbane **510** (Scheme 146).[210]



Scheme 144



Scheme 145

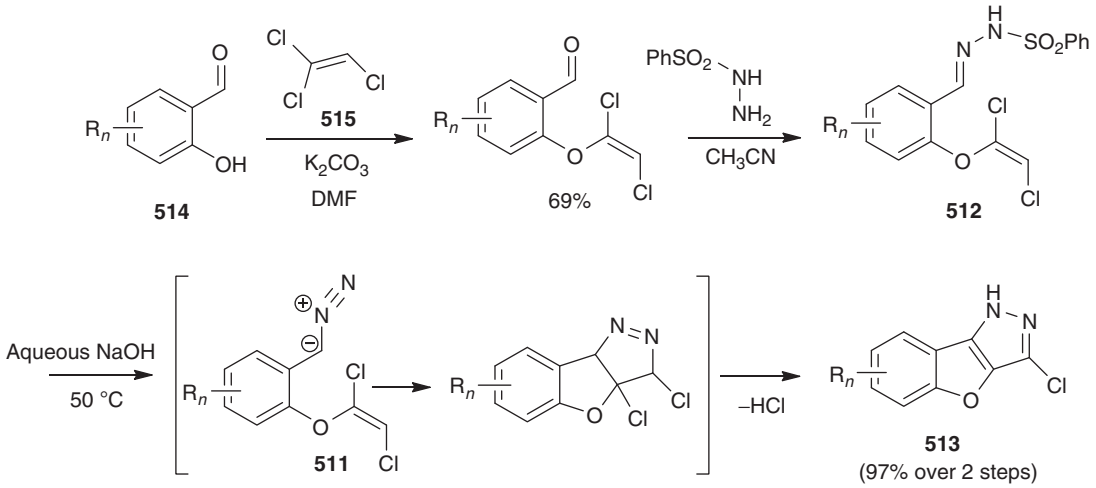


Scheme 146

4.21.9 Miscellaneous Dipoles

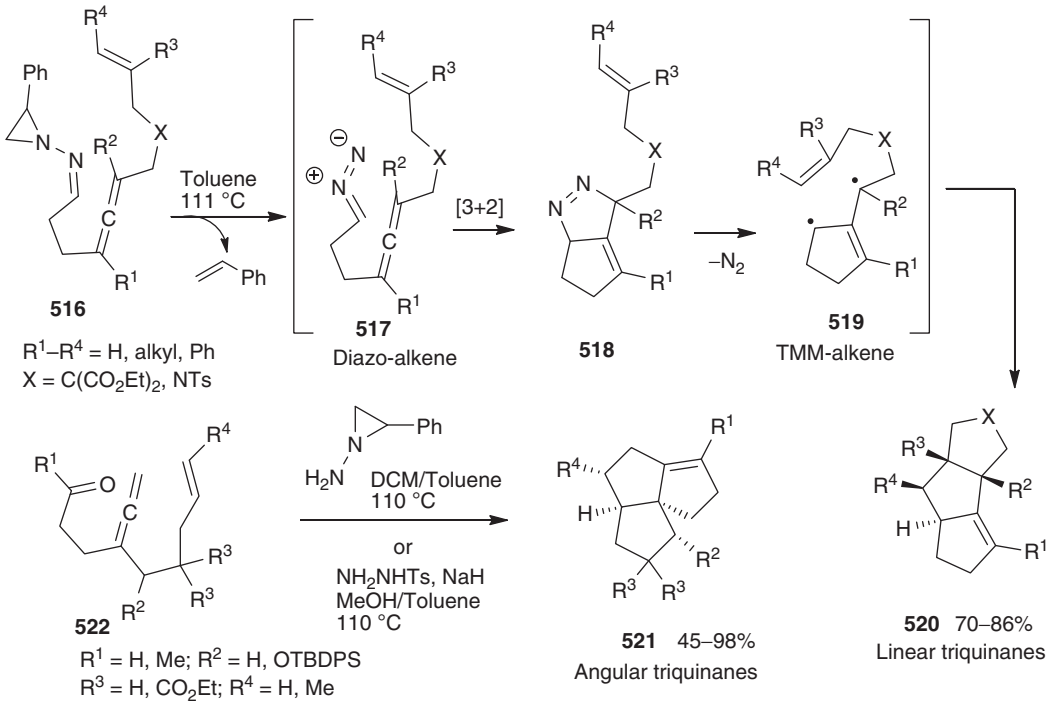
In addition to the reactions of 1,3-dipoles described earlier, isolated, yet notable examples of IDC reactions of a number of other dipolar species can be found in chemical literature. A few selected examples of such IDC reactions are described in the following paragraphs.

IDC reaction of diazo compounds **511**, generated by base treatment of salicylaldehyde-derived hydrazones **512** furnished benzofuropyrazoles **513** as the final products. The dichlorovinyloxy (dipolarophile) unit was, in turn, installed by the reaction of salicylaldehydes **514** with trichloroethylnene **515** (Scheme 147). The entire sequence of reactions from salicylaldehydes to the benzofuropyrazoles could also be carried out in one-pot by judicious choice of the base and solvent.[211]



Scheme 147

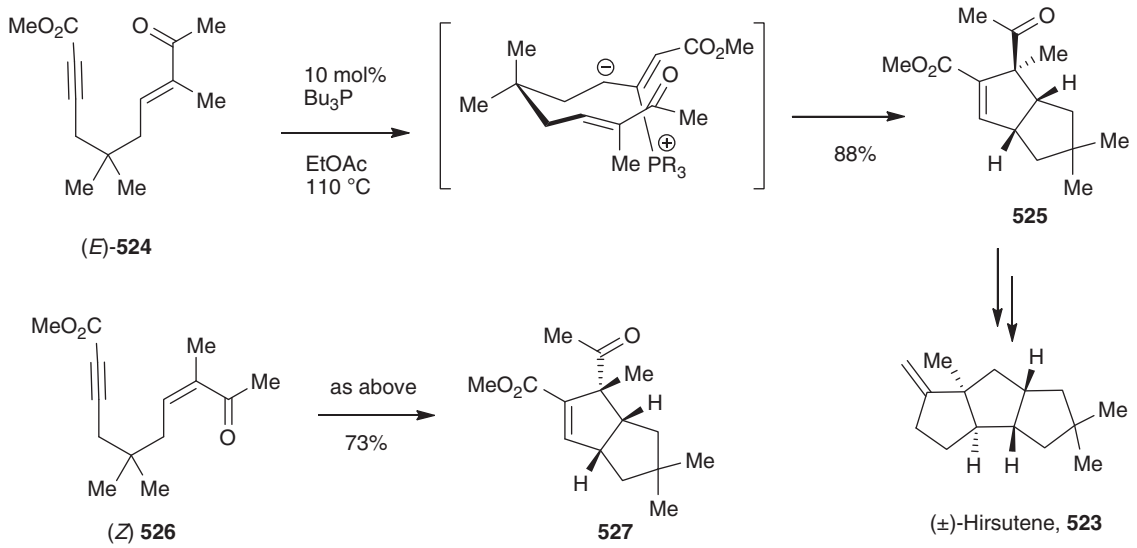
Linear and angular triquinane structural frameworks, widely found in naturally occurring terpenes, have been constructed by means of a tandem dipolar cycloaddition sequence of variously substituted allenes. Thermal extrusion of styrene converted the aziridinyl imine **516** into a transient diazo compound **517** which underwent an initial dipolar cycloaddition to the tethered allene



Scheme 148

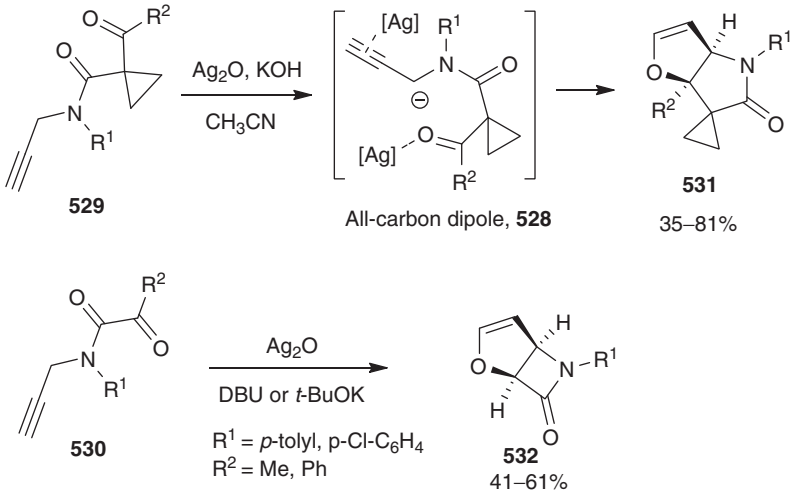
to produce the dihydropyrazole **518**. This is followed by facile nitrogen extrusion to generate a trimethylenemethane (TMM) diyl **519**. The latter readily reacted with the terminal alkene in a formal [2+3] cycloaddition to furnish the linear triquinane **520** in high yields and complete diastereoselectivity (Scheme 148). The angular triquinane **521** was obtained from the keto-allene **522** in an analogous fashion. When the tether length between the allene and the aziridinyl imine unit was altered, pyrazole derivatives resulting from the initial diazoallene cycloaddition were obtained, thereby providing indirect evidence for the proposed reaction pathway.[212]

Stereoselective phosphine-catalyzed intramolecular [3+2] cycloaddition reactions of alkynyl esters with enones have been reported to afford diquinane derivatives.[213] This elegant approach was applied in a total synthesis of the linear triquinane, hirsutene **523**. The interaction of the linear substrate **524** with catalytic amounts of tributylphosphine afforded the desired cycloadduct **525** in 88% yield as a single diastereomer. Three contiguous stereocenters, including a quaternary one, are installed with complete control during the cyclization. Remarkably, when the corresponding *Z* isomer **526** was subjected to identical reaction conditions, *epi*-diquinane derivative **527** was obtained as the sole product confirming the stereospecificity of the cycloaddition. Hirsutene was synthesized in a few steps from the cycloadduct **525** (Scheme 149).[214]



Scheme 149

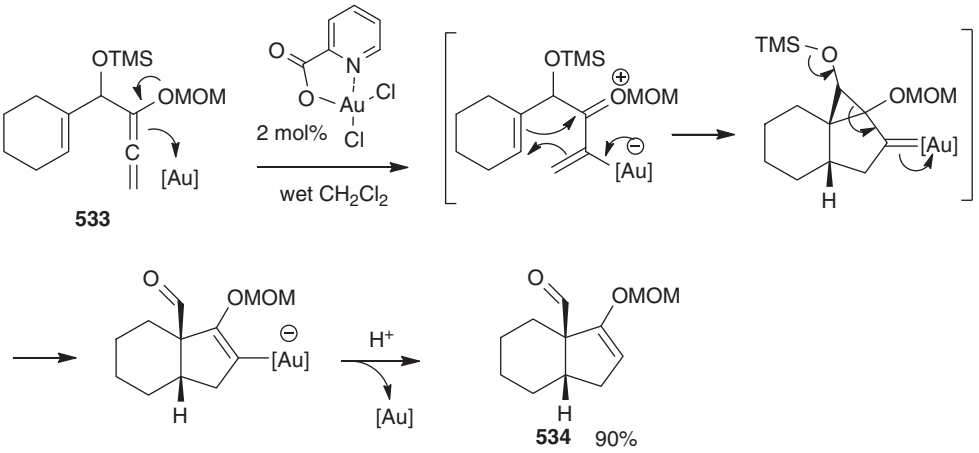
A formal 1,3-dipolar cycloaddition catalyzed by silver oxide involving all carbon 1,3-dipoles (e.g., **528**) generated from oxo-*N*-propargyl amides **529–530** led to the formation of furo[3,2-b]-*β*-lactams **531** and furo[3,2-b]-*γ*-lactams **532** (Scheme 150).



Scheme 150

Depropargylation of the starting materials was also observed to some extent, presumably occurring via silver-catalyzed isomerization to the corresponding allenamide and subsequent hydrolysis.[215]

Cyclopentenone enol ethers **533** containing all-carbon quaternary centers were synthesized via a gold-catalyzed intramolecular formal [3+2] cycloaddition of allenyl ethers **534** with tethered alkenes. A representative example is depicted in **Scheme 151**. The cyclization is completely stereoselective and proceeds under mild conditions.[216]



Scheme 151

4.21.10 Conclusions and Outlook

The combination of a dipole, dipolarophile, and a tether, three variable motifs, endows IDC reactions with a great degree of exceptional versatility that is generally associated with multicomponent processes. Unactivated olefins and alkynes participate much more efficiently in IDC reactions when compared to the intermolecular variants. Therefore, functional group noncompatibility issues that plague many other synthetic protocols are less of a concern in IDC reactions. As one would expect, the availability of a significant number of 1,3-dioples of well-studied chemistry allows for the preparation of a variety of heterocycles via the IDC reactions. More significantly, by varying the nature of the tether (all-carbon or heteroatom-containing) and length, a diverse array of carbocyclic and heterocyclic scaffolds can be assembled via IDC reactions. The steady progress made in the realm of 1,3-dipolar cycloadditions since Huisgen's seminal discovery in 1963, has provided convenient experimental protocols for the generation of various transient 1,3-dipoles, better understanding of the reactivity patterns of various dipole–dipolarophile combinations, and newer synthetic applications of the cycloadducts. Therefore, it is not surprising that more and more applications of IDC reactions as key transformations in natural product syntheses have appeared in the last two decades. As described in previous sections, IDC reactions have played important roles in the syntheses of alkaloids, terpenoids, carbohydrates, various natural product analogs, and application-oriented designer compounds. It is reasonable to assume that efforts along this line will be continued for years to come. New protocols for 1,3-dipole generation, increased focus on asymmetric transformations, newer applications of various cycloadducts, macrocyclic constructions, and higher order intramolecular dipolar cycloaddition reactions constitute some of the areas that are likely to enrich this pivotal area of organic synthesis.

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4.22 Intermolecular 1,3-Dipolar Cycloadditions of Alkenes, Alkynes, and Allenes

L-J Wang and Y Tang, Shanghai Institute of Organic Chemistry, Shanghai, China

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Glossary

Click chemistry A modular synthetic approach toward the assembly of new molecular entities by efficiently and reliably joining small units together. By applying this concept, it becomes possible to produce manmade compounds of vastly greater diversity than what is currently known or available.

Dipolarophile A compound (most often alkenes) that reacts with 1,3-dipoles in a cycloaddition reaction.

1,3-Dipole In organic chemistry, a 1,3-dipolar compound or 1,3-dipole is a dipolar compound with delocalized electrons and a separation of charge over three atoms.

Inverse electron demand 1,3-dipolar cycloaddition A 1,3-dipolar cycloaddition reaction of a 1,3-dipole with an electron-rich alkene that requires a dominant interaction of the lowest unoccupied molecular orbital $(\text{LUMO})_{\text{1,3-dipole}}$ with the highest occupied molecular orbital $(\text{HOMO})_{\text{dipolarophile}}$.

Organocatalyst A small organic compound that functions as a catalyst in organic reactions, related to the activation mechanisms of covalent binding of the substrate or noncovalent interactions such as hydrogen bonding.

4.22.1 Introduction

The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition or Huisgen reaction,[1] is a reaction belonging to a large class of concerted, pericyclic cycloadditions between a 1,3-dipole and a dipolarophile, most of which are substituted alkenes, alkynes, and allenes to form a five-membered ring (Scheme 1) (*see* Chapter 4.21).

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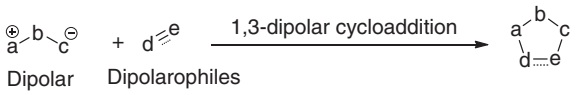


Scheme 1

Huisgen has classified the 1,3-dipoles into allyl and propargyl types (Figure 1).[2] The allyl type 1,3-dipoles are bent, which have a system of 4π-electrons in three parallel atomic *pz* orbitals. However, the propargyl-type 1,3-dipoles, which contain a triple bond, have a linear structure. In the past two decades, a plenty of 1,3-dipoles containing various combinations of carbon and heteroatoms have attracted much attention and their reactions with versatile dipolarophiles have been developed vigorously, especially in the asymmetric catalysis field. Some of these reactions have been well reviewed.[3] In this chapter, the researchers wish to describe the recent progress on the intermolecular cycloaddition reactions of important 1,3-dipoles from both types, including nitrones, carbonyl ylides, azomethine ylides, azomethine imines, nitrile oxides, nitrile imines, diazoalkanes, and azides, beyond the coverage of a review published in 1991.

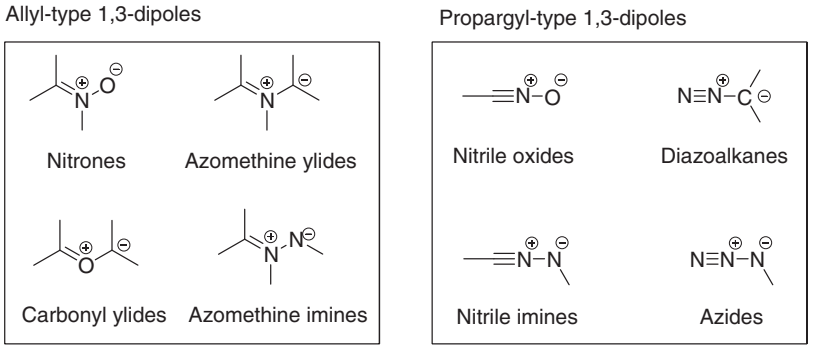
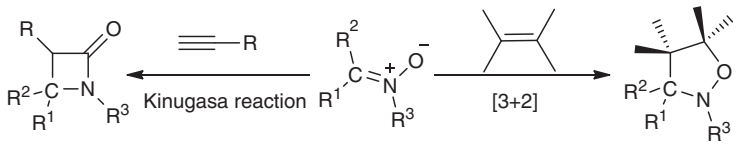


Figure 1 Classification of the 1,3-dipoles.

4.22.2 Nitrones

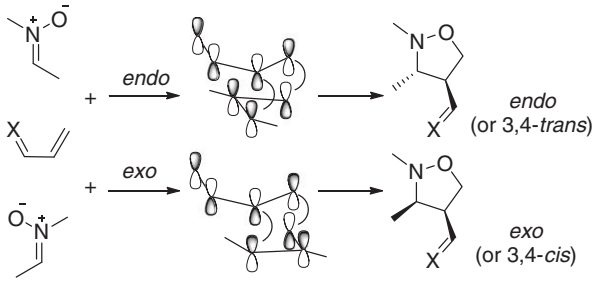
As the *N*-oxide of an imine, the general structure of nitrone is $R^1R^2C{=}N^+R^3O^-$, where R^3 is different from H. Nitrones are one of the most important synthetically useful 1,3-dipoles in 1,3-dipolar cycloadditions. They react with various alkenes and alkynes to form isoxazolidines and β-lactams (Scheme 2), which are valuable functional groups in organic chemistry.



Scheme 2

4.22.2.1 Control of *exo*/*endo*-Selectivity in Asymmetric Catalytic 1,3-Dipolar Cycloaddition Reaction of Alkenes with Nitrones

The 1,3-dipolar cycloaddition reaction of alkenes with nitrones, which provides access to isoxazolidines bearing two or three asymmetric centers is a well-known protocol in organic chemistry and has attracted extensive study.[4] Among those literatures documented on this topic, the most interesting and challenging aspect of this reaction is to control both the *exo*/*endo*-selectivity and enantioselectivity of the cycloaddition (Scheme 3). Generally, the typical Diels–Alder reaction undergoes an *endo*-dominant transition state (TS), which is stabilized by the secondary π orbital interactions (*see* Chapter 5.09). However, in the 1,3-dipolar cycloaddition reaction of alkenes with nitrones, this stabilization is smaller. Therefore, the *endo*/*exo*-selectivity in the 1,3-dipolar cycloaddition reaction is primarily controlled by the factors of stereoenvironment in the reaction transition state, for instance, the structure of the substrates or catalysts.[5]

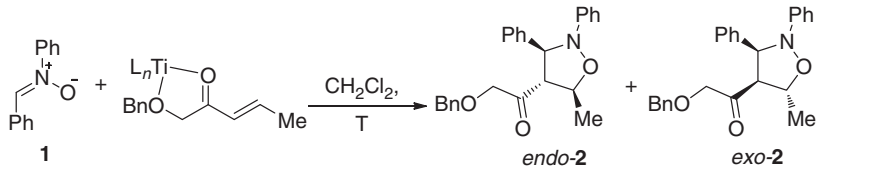


Scheme 3

4.22.2.1.1 Electron-deficient alkenes

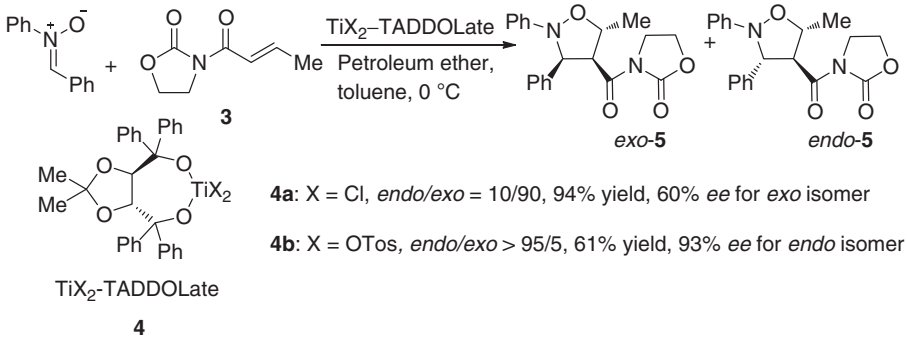
Generally, in the 1,3-dipolar cycloaddition reaction of nitrones with alkenes, regioselectivity presents. For reactions between nitrones and electron-deficient alkenes, it is controlled by a highest occupied molecular orbital $(HOMO)_{dipole}$–lowest unoccupied molecular orbital $(LUMO)_{alkene}$ interaction. Electron-deficient alkenes, such as enamides, enals, and enones are extensively used, leading to various five-membered cyclic adducts, which are synthetically useful compounds in organic chemistry.

Pioneering work in stereoselective 1,3-dipolar cycloaddition reactions was developed by Kanemasa et al. in 1992.[6] An enone containing an α-benzyloxy group was employed to react with nitrone **1** (Scheme 4). This reaction needs a stoichiometric amount of $TiCl_2(O^iPr)_2$ as Lewis acid to activate the LUMO of the alkene and give the *endo*-**2** isomer exclusively at 0 °C. However, this reaction was also controlled by thermodynamics. When the reaction proceeds at 80 °C in the absence of metal complex, a mixture of *endo*/*exo*-isomer was obtained. In the following two decades, much effort has been paid to the control of *exo*/*endo*-selectivity as well as the stereoselectivity, and the 1,3-dipolar cycloaddition of nitrones has become of great interest in organic synthesis.



Scheme 4

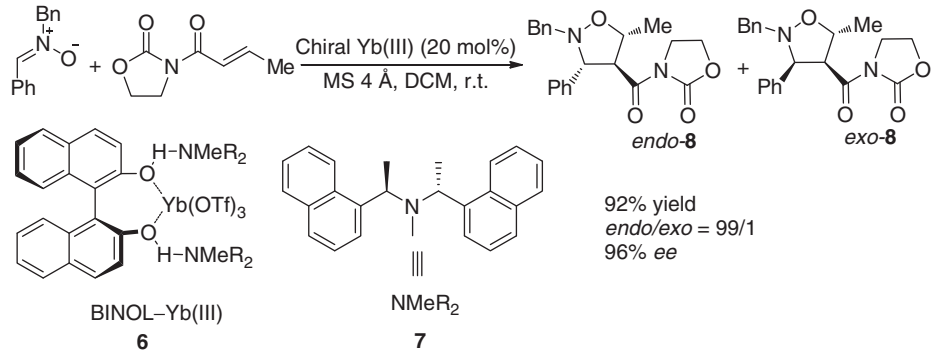
The enamides bearing oxazolinone moiety proved to be favorable dipolarophiles due to the bidentate-coordinating sites, which could easily be activated by Lewis acid. The first highly diastereo- and enantioselective titanium-catalyzed 1,3-dipolar cycloaddition reaction of 3-((*E*)-2′-alkenoyl)-1,3-oxazolidin-2-ones **3** with nitrones has been described by Jørgensen and co-workers.[5,7] When the $TiCl_2$–TADDOLate catalysts **4a** were employed to catalyze the 1,3-dipolar cycloaddition reaction of alkenes with nitrones, the *exo*-**5** isomer of the isoxazolidines was obtained with up to 60% *ee*. When tosylate was accommodated instead of the chloride, the *endo*-**5** isomer was obtained with 93% *ee* in a diastereoselectivity of >90% (Scheme 5).



Scheme 5

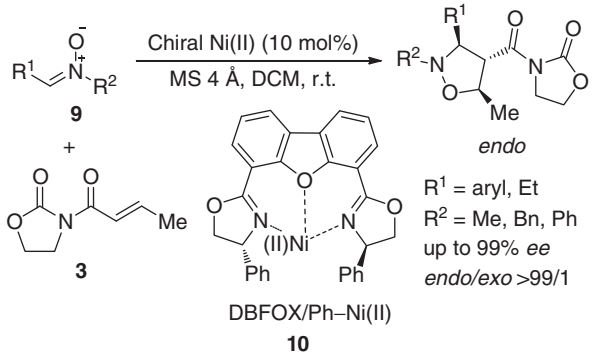
Kobayashi et al. developed a novel heterochiral Yb(III) catalyst in the catalytic enantioselective 1,3-dipolar cycloaddition reaction. With 20 mol% of $Yb(OTf)_3$–BINOL complex **6** in the presence of chiral tertiary amine **7**, the reaction proceeded well to

give *endo*-**8** as the major product (Scheme 6).[8] In this reaction, the chiral amine binding to the phenolic hydrogen of the BINOL–Yb(III) complex by hydrogen bonding, which was confirmed by the infra-red spectra, is essential for the high enantiocontrol.



Scheme 6

Kanemasa et al. studied asymmetric catalytic 1,3-dipolar cycloaddition reaction of nitrone **9** with 3-((*E*)-2′-alkenoyl)-1,3-oxazolidin-2-ones **3**.[9] A DBFOX/Ph–Ni(II) complex **10** resulted in near perfect *endo*-selectivity (*endo*/*exo* > 99/1) with >99% *ee* (Scheme 7). In this reaction, the presence of molecular sieve (MS) 4 Å is critical for both *endo*- and enantioselectivities.



Scheme 7

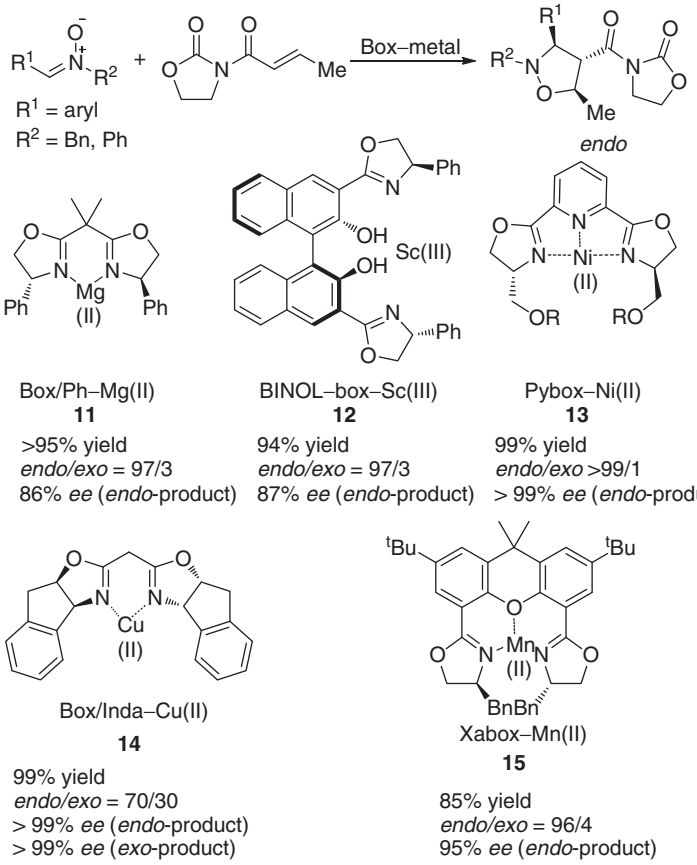
A variety of chiral bisoxazoline (BOX)–metal complexes,[10] such as Ph–BOX–Mg(II) **11**,[10a] BINOL–BOX–Sc(III) **12**,[10b] pyBOX–Ni(II) **13**,[10c–e] In–BOX–Cu(II) **14**,[10g] and xaBOX–Mn(II) **15**,[10f] are efficient catalysts for the asymmetric 1,3-dipolar cycloaddition reactions of nitrones with enamides, affording the major *endo*-isomer with high enantioselectivity (Scheme 8).

In contrast to the *endo*-selectivity preference in the previous work, Sibi et al. reported an *exo*-selective enantioselective 1,3-dipolar cycloaddition of nitrones in 2004.[11] It was believed that the Lewis acid that forms square planar complexes plays a key role to control the *exo*-selectivity. A stereochemical model was demonstrated in Figure 2 (for olefin substrate, nitrone, and ligand–copper(II) complex), in contrast to the *endo*-attack, the *exo*-mode attack is more favored due to the steric reason. This catalyst system could be extended to *α*,*β*-disubstituted N–H acrylimide dipolarophiles, leading to high *exo*-selectivity and enantiocontrol.

By using chiral binaphthyldiimine (BINIM)-Ni(II) complex **17** as catalyst, Suga et al. have developed an asymmetric catalytic 1,3-dipolar cycloaddition reaction of nitrones with 3-(2-alkenoyl)-2-thiazolidinethiones **16** (Scheme 9).[12] It is noteworthy that this methodology provides *exo*-**18** as the major isomer along with high enantioselectivity for a number of nitrones.

The 1,3-dipolar cycloaddition of nitrone to olefin was catalyzed by a cationic TolBINAP–palladium(II) complex **19** resulting in moderate to excellent yield and good enantioselectivities for the corresponding isoxazolidine derivatives **21**.[13] It was believed that the *endo*/*exo*-selectivity of the products depends on the *N*-substituent group of nitrones **20**. With benzyl-substituted nitrone **20a**, the reaction resulted in 97/3 *endo*/*exo*-selectivity. However, the reaction gave 28/72 *endo*/*exo*-selectivity and poor enantiocontrol when phenyl-substituted nitrone **20b** was employed (Scheme 10).

Other bidentate electron-deficient alkenes have been developed as suitable dipolarophiles in the 1,3-dipolar cycloaddition reaction. Palomo et al. have documented that *α*-hydroxy enone **22** as dipolarophile reacts with nitrones smoothly under the catalysis of bis(oxazoline)–Cu(II) complex **23**,[14] leading to cycloadducts with very high levels of *endo*- and enantioselectivities (Scheme 11).



Scheme 8

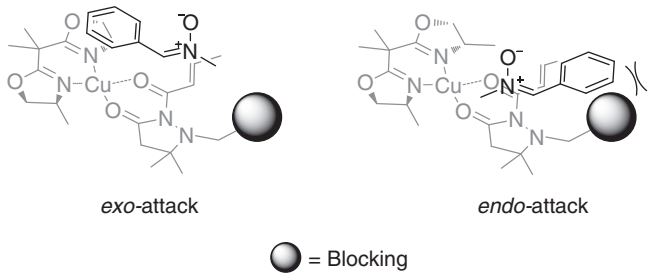
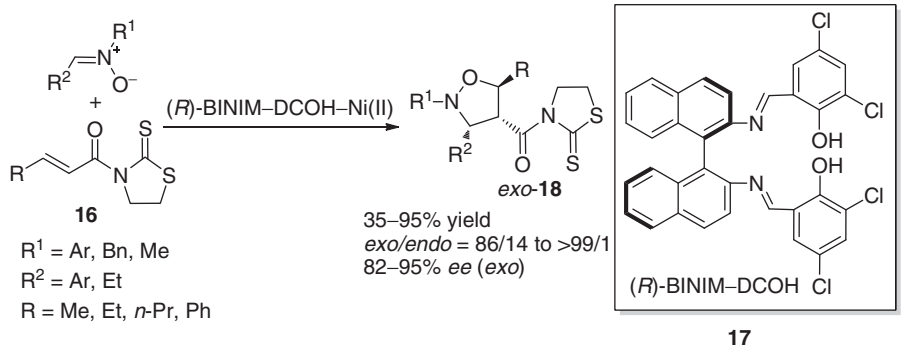
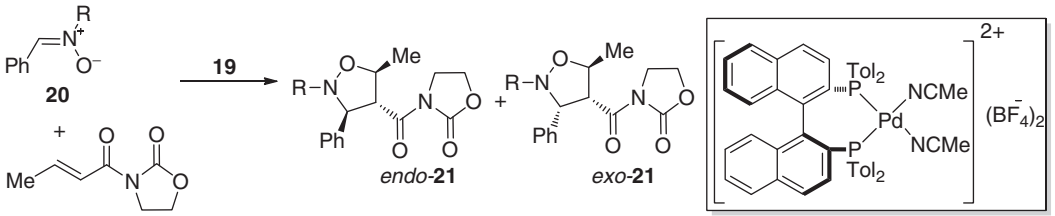


Figure 2 Stereochemical model for *exo*-selective 1,3-dipolar cycloaddition.



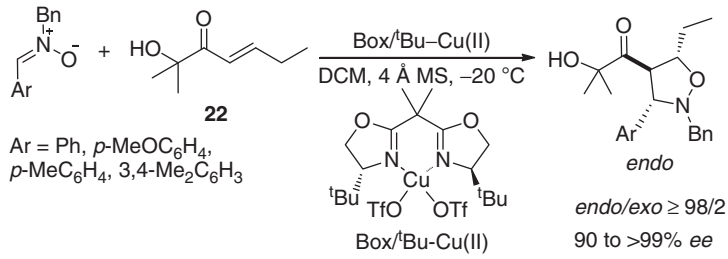
Scheme 9



21a: R = Bn, *endo/exo* = 97/3, 94% yield, 89% *ee* (*endo*)
21b: R = Ph, *endo/exo* = 28/72, 94% yield, 48% *ee* (*exo*)

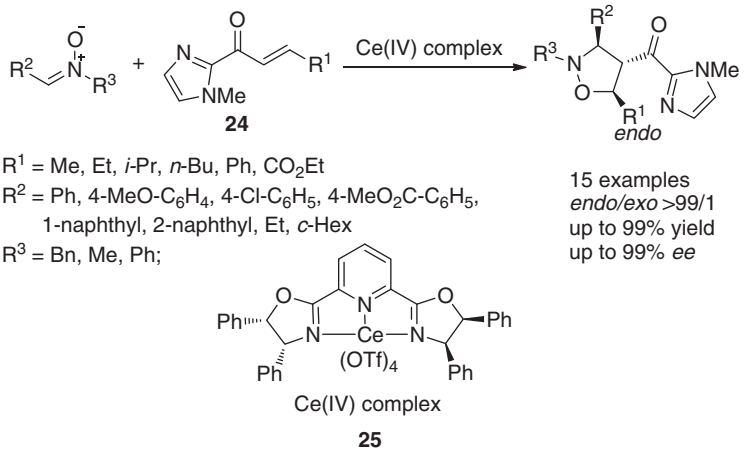
(*S*)-TolBINAP–Pd(II) **19**

Scheme 10



Scheme 11

Evans et al. employed the α,β-unsaturated 2-acyl imidazoles **24** in the asymmetric 1,3-dipolar cycloaddition reaction with nitrones catalyzed by Ce(IV)–*cis*-bis-PhpyBOX complex **25** producing an excellent substrate scope under mild reaction conditions in a preference of *endo*-selectivity (Scheme 12).[15]

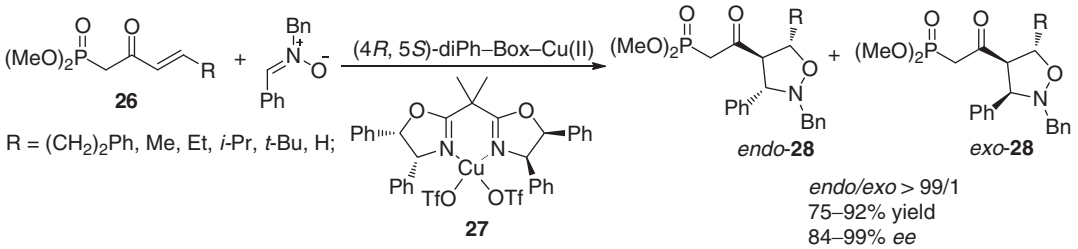


Scheme 12

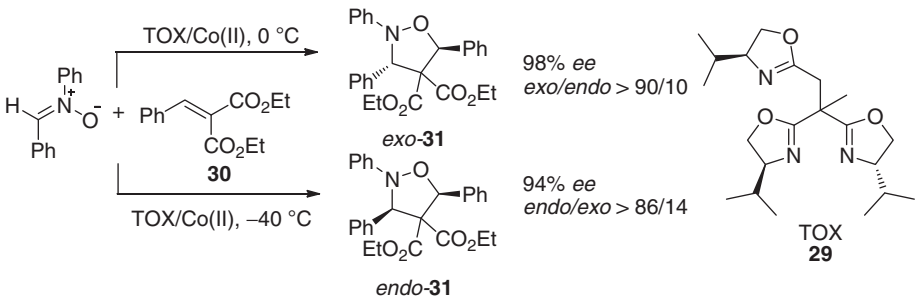
Kim et al. have found that the β-phosphoric enone **26** bidentate template is highly efficient for the catalytic asymmetric 1,3-dipolar cycloaddition of nitrones.[16] Using the chiral Lewis acid, $Cu(OTf)_2$/(4*R*,5*S*)–diPh–BOX **27** as the catalyst, the isoxazolidine adducts **28** were obtained in high yield with >99/1 *endo*/*exo*-selectivities and high enantioselectivities (Scheme 13).

Tang et al. have developed Co(II)–trisoxazolines (TOX) **29** for the enantioselective cycloaddition between nitrones and alkylidene malonates **30**.[17] The outstanding character of this catalyst system is that the *endo*/*exo*-selectivity could be controlled effectively by running the reaction at 0 or −40 °C and thus both *exo*- and *endo*-isoxazolidine **31** could be prepared enantioselectively (Scheme 14).

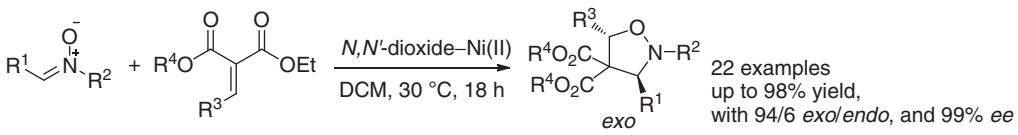
Recently, Feng et al. applied chiral nickel(II)/*N*,*N*′-dioxide complex **32** developed in their own group in the asymmetric 1,3-dipolar cylcloaddition reaction of nitrones to alkylidene malonates, producing the cycloadducts in good yield with excellent *exo*- and enantioselectivities (up to 98% yield, with 94/6 *exo*/*endo*, and 99% *ee*)[18](Scheme 15).



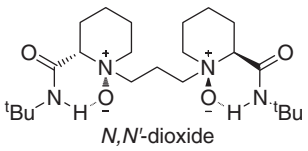
Scheme 13



Scheme 14

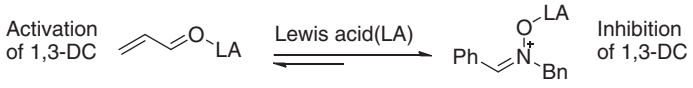


R^1 = Ph, *o*-$NO_2C_6H_4$, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, 2-naphthyl
R^2 = Me, Ph, Bn
R^3 = Ph, *p*-$NO_2C_6H_4$, *p*-BrC_6H_4, *m*-ClC_6H_4, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, 2-naphthyl, 2-thienylcyclohexyl
R^4 = Et, Me, *i*-Pr, *t*-Bu, Bn



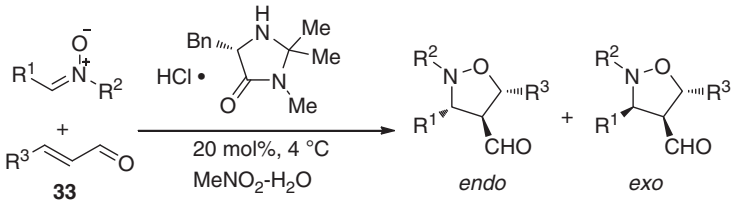
Scheme 15

The 1,3-dipolar cycloaddition reaction between nitrones and α,β-unsaturated aldehydes provides isoxazolidines bearing a convertible formyl group, which are useful synthons for the construction of biologically valuable amino acids, β-lactams, amino carbohydrates, and alkaloids. However, α,β-unsaturated aldehydes containing monodentate carbonyl, which has less coordinating ability with Lewis acids compared with bidentate ones, were challenging substrates in metal-catalyzed nitrone cycloadditions, probably because of the competitive coordination of Lewis acids between nitrone oxides and aldehydes (Scheme 16).[19]



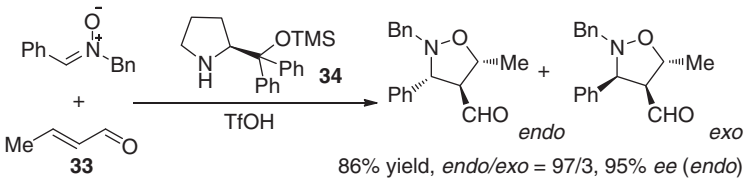
Scheme 16

MacMillan et al. have developed an amine catalyst system, which is inert to nitrone association, to undergo an iminium activation of the α,β-unsaturated enal **33**, and realize the first example of enantioselective organocatalytic 1,3-dipolar cycloaddition reaction (Scheme 17).[19] Fifteen examples have been demonstrated, and the products are obtained in 66–98% yield with 90–99% *ee*'s and up to 99/1 *endo*/*exo*-selectivity.



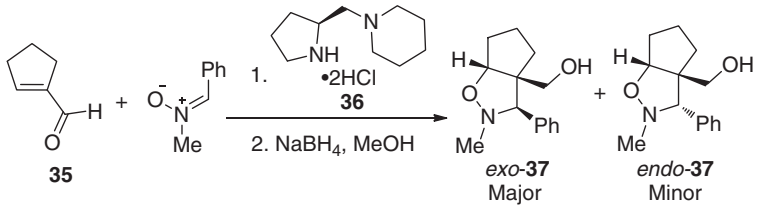
Scheme 17

L-Proline-derived organocatalysts are capable of promoting the 1,3-dipolar cycloaddition of nitrone with α,β-unsaturated aldehyde by iminium activation mechanism.[20] Nevalainen et al. reported that the diphenyl-L-prolinol trimethyl silyl ether **34** catalyzed the cycloaddition of nitrones to crotonaldehyde **33**, providing isoxazolidines in high yield with 97/3 *endo*/*exo* and 95% *ee* (Scheme 18).[20a] A highly enantioselective organocatalytic three-component reaction between *N*-arylhydroxylamines, aldehydes, and α,β-unsaturated enals has been developed by Córdova et al.[20b] The reaction provides an approach to isoxazolidines in high yield with >25/1 *endo*-selectivity and 91–99% *ee*.



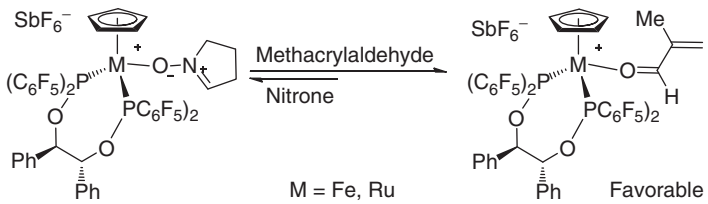
Scheme 18

Using chiral pyrrolidine salts **36a** as catalyst, the 1,3-dipolar cycloadditions of nitrones with 1-cycloalkene-1-carboxaldehydes **35** have been documented by Karlsson et al., furnishing fused *exo*-bicyclic isoxazolidines *exo*-**37** with high diastereo- and enantioselectivities (Scheme 19).[21]



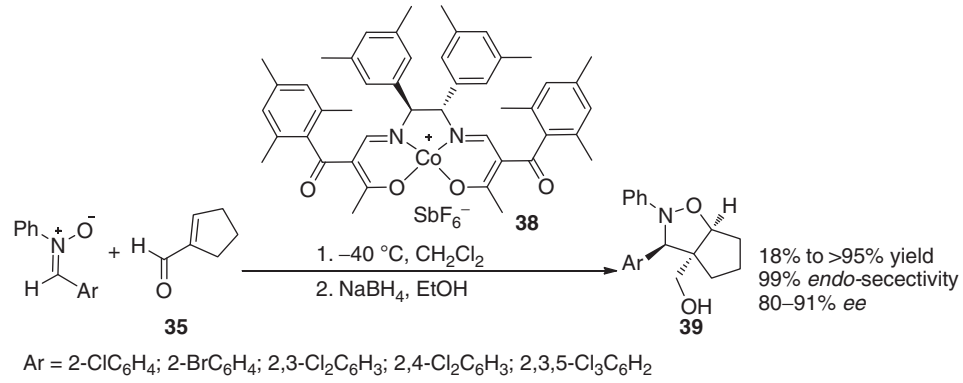
Scheme 19

Kündig et al. have shown that a single coordination site transition metal complex, such as Fe- and Ru-Lewis acid, can efficiently catalyze the asymmetric 1,3-dipolar cycloadditions of nitrones with α,β-unsaturated enals.[22] It was believed that the aldehyde-selective chiral Lewis acid site was likely to be able to discriminate between enals and nitrones. The chiral complex prefers to coordinate with the aldehydes, or to bind to nitrones in a readily reversible manner in the preference of aldehyde over nitrone (Scheme 20). Good to high enantioselectivities and high yield were obtained for cyclic nitrones and various α,β-unsaturated enals in good to high *endo*-selectivities.



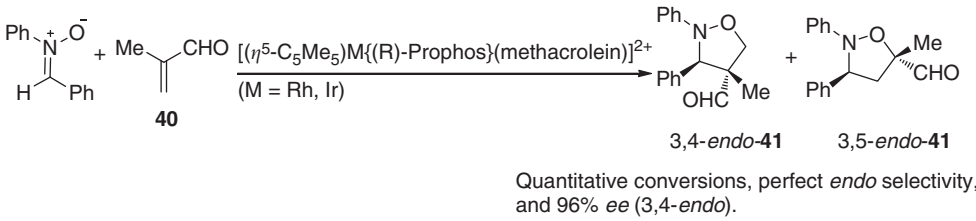
Scheme 20

Yamada et al. have developed enantioselective 1,3-dipolar cycloaddition reaction of 1-cyclopentene-1-carbaldehyde **35** with nitrones, which employed optically active *β*-ketoiminato cationic cobalt(III) complex **38** as efficient Lewis acid catalyst.[23] The corresponding products were *in situ* reduced by transformation of the aldehyde in the resulting cycloadduct into stable primary alcohol **39**, and excellent *endo*- and high enantioselectivities (80–91% *ee*) were achieved (Scheme 21).



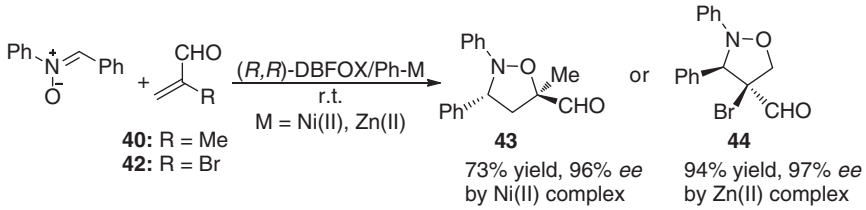
Scheme 21

Camona et al. have documented a rhodium- or iridium-based system in which the activation of the electron-deficient monofunctionalized alkene by catalyst is favored with respect to nitrone coordination.[10h,24] 1,3-Dipolar cycloaddition reaction of nitrones with methacrolein **40** was achieved, leading to isoxazolidines **41** in full conversion, perfect *endo*- and excellent enantioselectivities (Scheme 22).



Scheme 22

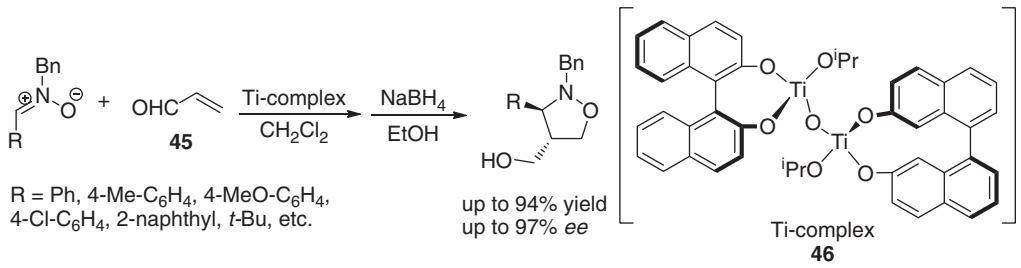
Kanemasa et al. have reported on the chiral Ni(II)-(*R,R*)-DBFOX/Ph complex catalyzed 1,3-dipolar cycloadditions of nitrones with *α*-alkyl- and *α*-arylacroleins **40** to produce the sterically controlled isoxazolidine-5-carbaldehydes **43** in up to 96% *ee*. On the basis of their theoretical study on Lewis acid-catalyzed nitrone cycloadditions,[25a] stronger Lewis acid favors the preferred formation of electronically controlled cycloadducts. With zinc(II)–(*R,R*)–DBFOX complexes the reactions of *α*-bromoacrolein **42** are effectively catalyzed to produce the electronically controlled isoxazolidine-4-carbaldehydes **44** in up to 97% *ee* (Scheme 23).[25c]



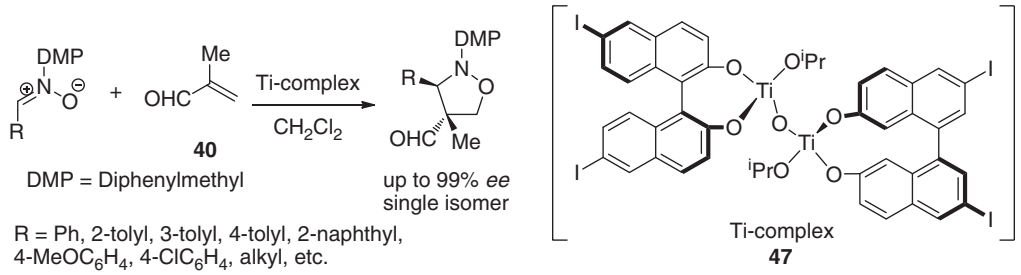
Scheme 23

In 2005, Maruoka and coworkers have developed an asymmetric 1,3-dipolar cycloaddition reaction between various nitrones and acrolein **45** catalyzed by a *μ*-oxo-type chiral bis-Ti(IV) oxide BINOLate complex **46**, furnishing the corresponding *endo*-isoxazolidines with up to 97% *ee* (Scheme 24).[26]

In 2007, they have also succeeded in the 3,4-*endo*-selective asymmetric 1,3-dipolar cycloadditions of nitrones and methacrolein **40** by the use of chiral bis-titanium Lewis acid **47** (Scheme 25).[27] The key to the success is the introduction of a bulky *N*-substituent on nitrone to attenuate the undesired Lewis acid–nitrone complexation. This strategy offers a new benchmark reaction for the chiral Lewis acid-catalyzed asymmetric 1,3-dipolar cycloadditions of nitrones.



Scheme 24



Scheme 25

4.22.2.1.2 Electron-rich alkenes

For 1,3-dipolar cycloaddition reactions between nitrones and electron-rich alkenes, it is controlled by a $LUMO_{dipole}$–$HOMO_{alkene}$ interaction. The *endo*/*exo*-selectivity could be controlled by Lewis and Brønsted acid catalysts. The difference between the above two catalysis systems is displayed in the TS models (Figure 3).[28] For the Lewis acid-catalyzed cycloadditions, the *exo*-approach (TS1) of the alkyl vinyl ether to the nitrone substrate is more favored than the *endo* approach (TS2) due to the steric repulsion between the alkoxy group and the bulky Lewis acid. For the Brønsted acid-catalyzed cycloadditions, the acidic proton is much smaller than the Lewis acid, which allows the alkyl vinyl ether to access in an *endo*-selective way (TS3). However, the *exo*-approach (TS4) might be disfavored because of the steric hindrance between the alkoxy and R^1 groups.

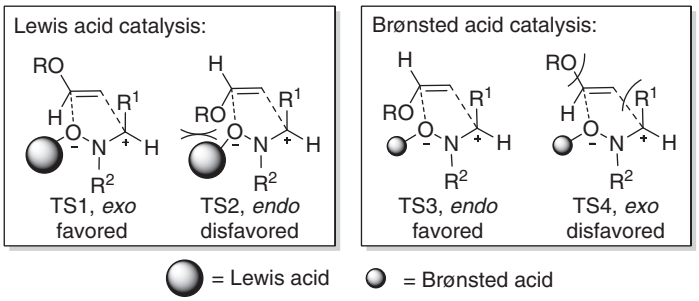
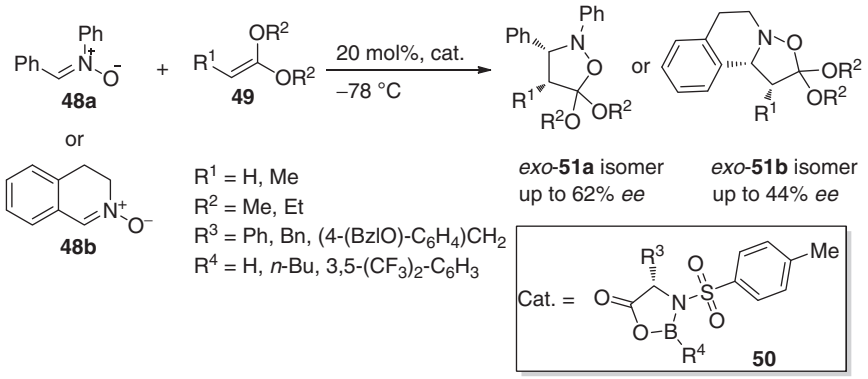


Figure 3 Transition-state models of Lewis acid and Brønsted acid catalysis system.

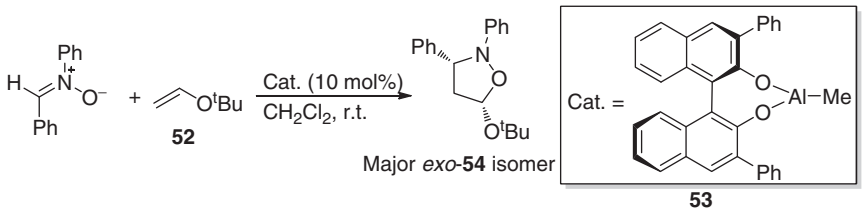
Pioneered by Scheeren et al.,[29] the asymmetric 1,3-dipolar cycloaddition of acyclic **48a** and cyclic **48b** nitrones with ketene acetals **49** has been reported in the catalysis of chiral oxazaborolidines **50** derived from *N*-tosyl-L-*α*-amino acids, giving the *exo*-**51a** isomer of 5,5-dialkoxyisoxazolidines in high yield with high stereoselectivity and up to 62% *ee* (Scheme 26).[29a] Dramatic solvents effect on the enantioselectivity of this asymmetric 1,3-dipolar cycloadditions with ketene acetals has been observed.[29b] The chiral oxazaborolidine could also catalyze the 1,3-dipolar cycloaddition reactions of nitrones with alkyl vinyl ethers and 2,3-dihydrofuran, but with low enantioselectivity.[29c,30]

Jørgensen et al. have successfully realized the asymmetric 1,3-dipolar cycloaddition reaction of nitrones with electron-rich alkenes such as vinyl ethers **52**, which was catalyzed by 3,3′-diaryl-BINOL–AlMe complexes **53**.[28a,31] A general activation mode for nitrones by chiral Lewis acids has been developed. It has been found that the 1,3-dipolar cycloaddition of aromatic nitrones with vinyl ethers is performed in high *exo*-selectivity, giving the corresponding isoxazolidines **54** with up to 97% *ee* and up to >95/5



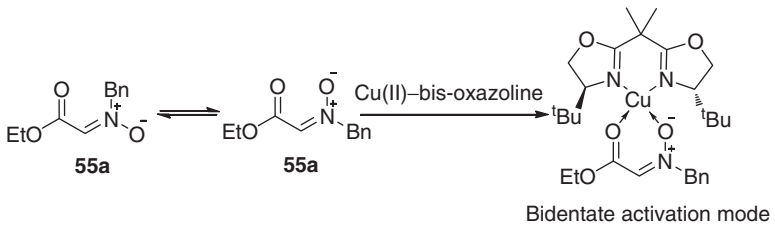
Scheme 26

exo/*endo*-selectivity (Scheme 27). The observed linear stereochemical effect between the *ee* of the catalyst and *ee* of the *exo*-product indicated that the catalytic intermediate consists of a discrete complex.



Scheme 27

A copper-BOX-catalyzed diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between electrophilic nitrones **55** and electron-rich alkenes has been developed by Jørgensen et al., in which the nitrones coordinated to the catalyst in a bidentate fashion (Scheme 28).[32] The reaction promoted smoothly with various alkenes under mild reaction conditions to give isoxazolidines in good yield, and up to 86/16 *exo*/*endo*-selectivity and with up to 94% *ee*.



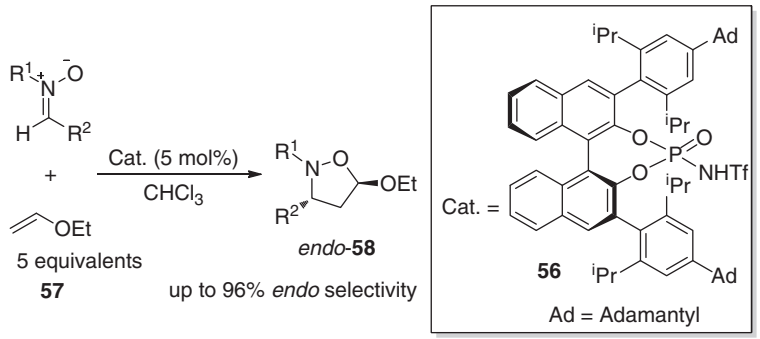
Scheme 28

Yamamoto et al. have reported the first asymmetric 1,3-dipolar cycloaddition of nitrones catalyzed by a chiral Brønsted acid.[28b] The chiral *N*-triflyl phosphoramide **56** catalyzed 1,3-dipolar cycloaddition of diaryl nitrones to ethyl vinyl ether **57** yielded the *endo*-**58** products as the major diastereoisomer (Scheme 29). Up to 96% *endo*-selectivity was obtained which was different from the previously reported up to >95% *exo*-selectivity of the AlMe–BINOL complex-catalyzed reaction.[28a]

4.22.2.1.3 Cyclopropanes

Recent studies on the 1,1-cyclopropane diesters involed reactions showed that the donor–acceptor cyclopropanes behaved similar to α,β-unsaturated carbonyl compounds in their ability to react with nucleophiles.[33] The strained bonds in the cyclopropane ring are believed to have π character-like alkenes. When the strained bond in 1,1-cyclopropane diester is polarized by coordination of Lewis acid, the cyclopropanes could be treated as one-carbon homologs of electron-deficient olefins, and could react with nitrones (Figure 4).[34]

Kerr et al. have reported that the cycloaddition reaction of donor–acceptor cyclopropanes **59** with nitrones, results in the formation of tetrahydro-1,2-oxazines **60** via a homo-[3+2] dipolar cycloaddition.[34,35]Additionally, the nitrones could be generated *in situ* by reaction of hydroxylamines **61** with aldehydes **62**. This three-component reaction provides the cycloadducts in a broad substrate scope with excellent diastereoselectivity (>95%) and yield (66–96%) (Scheme 30).



R^1 = Ph, *p*-ClC_6H_4, *p*-FC_6H_4
R^2 = Ph, *p*-ClC_6H_4, *p*-$CF_3C_6H_4$, *p*-$NO_2C_6H_4$, 3,5-$F_2C_6H_3$, 2-furyl, 2-thienyl

Scheme 29

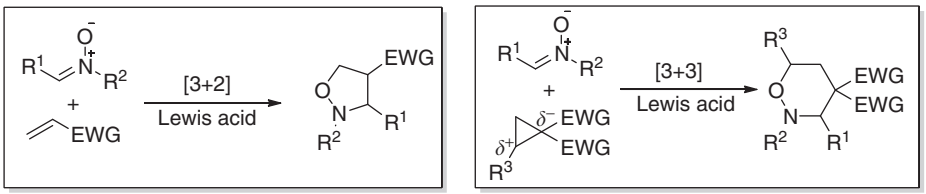
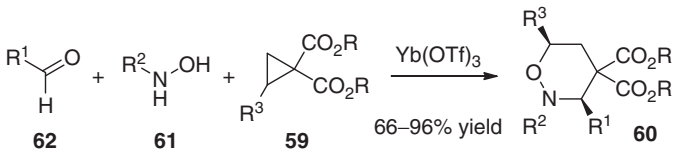


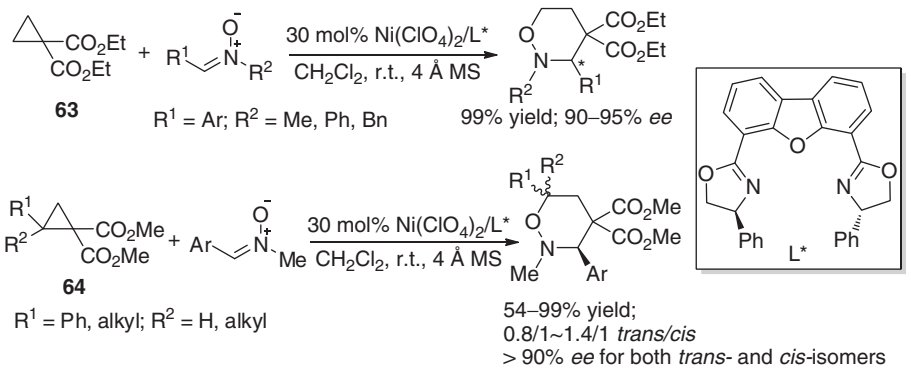
Figure 4 Cyclopropanes as homologs of electron-deficient olefins in 1,3-dipolar cycloaddition.



R^1,R^2,R^3 = aryl, alkyl

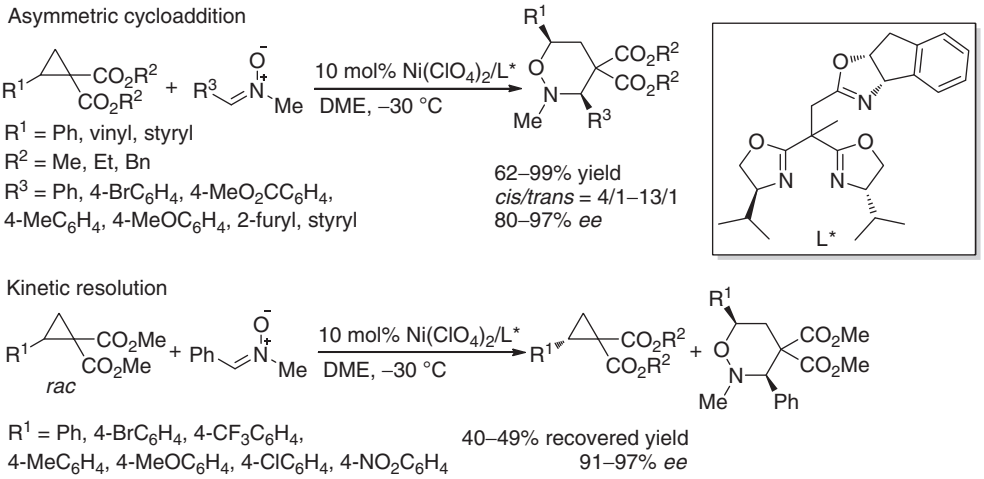
Scheme 30

The first examples of chiral Lewis acid-catalyzed asymmetric cycloaddition of cyclopropanes and nitrones have been demonstrated by Sibi et al., in the synthesis of tetrahydro-1,2-oxazines with very excellent enantioselectivity (for unsubstituted cyclopropane diesters **63**, 99% yield and 90–95% *ee*) (Scheme 31).[36] For reactions with racemic cyclopropane diesters **64**, excellent enantioselectivity could be obtained, but with approximately 1:1 diastereoselectivity. In terms of reactivity, the substituted cyclopropane diesters are much more reactive than the unsubstituted substrate.



Scheme 31

Tang et al. have developed a successful chiral trisoxazoline/Ni(II) catalytic system in the cycloaddition of 2-substituted cyclopropane-1,1-dicarboxylates with nitrones (Scheme 32).[37] High diastereoselectivity and 80–97% enantioselectivity have been achieved. The same catalyst could also be used in the kinetic resolution of two-substituted cyclopropane-1,1-dicarboxylates, affording the recovered chiral cyclopropanes in excellent *ee* values. Through asymmetric cycloaddition or a kinetic resolution/cycloaddition cascade, this protocol provided a convenient access to both enantiomers of tetrahydro-1,2-oxazines.

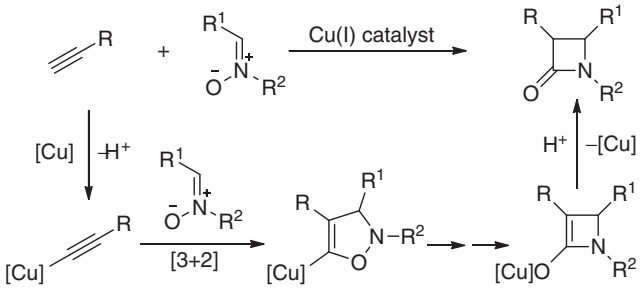


Scheme 32

4.22.2.2 Alkynes and Allenes

4.22.2.2.1 Kinugasa reaction

Four-membered heterocyclic compounds such as chiral *β*-lactams are key structures of many biologically active molecules and are also a type of useful and extensively employed synthetic intermediates in modern organic synthesis. Among the approaches for their asymmetric synthesis, the enantioselective catalytic Kinugasa reaction of alkynes with nitrones has attracted intensive studies, due to the readily available starting material and high atom economy (Scheme 33).[38,39]



Scheme 33

Inspired by the pioneering work of Kinugasa and Hashimoto,[40] Miura and coworkers disclosed the asymmetric catalytic version of the Kinugasa reaction in 1995 in the synthesis of 2-azetidinone with phenylacetylene and *N*,*N*-diphenylnitrone, using BOX**65**/CuI complex as catalyst and up to 57% *ee* was obtained (Figure 5).[41] Recently, BOX/Cu(I) catalyst system has been successfully applied to the enantioselective Kinugasa reactions. Evans and coworkers reported a highly stereoselective copper-catalyzed coupling reaction of alkynes with nitrones using IndaBOX ligand **66**, leading to up to 97:3 *dr* and 98% *ee*.[38f] IndaBOX ligand **67** was also employed by Saito and coworkers in a recent report.[42] In 2007, Guiry and coworkers applied thiophene oxazoline ligands HETPHOX **68** in the Kinugasa reaction and achieved a moderate level of enantioselectivity (up to 55% *ee*).[43]

The first highly enantioselective catalytic Kinugasa reaction was reported in 2002 by Fu and coworkers, in which good to high enantioselectivities (up to 93% *ee*) and high *cis*-selectivities (up to >95:5 *dr*) were obtained with C_2-symmetric bis(azaferrocene)$_2$ **69**/CuCl as the catalyst (Scheme 34).[44]

Tang and coworkers have developed trisoxazoline **70**/copper(II)-catalyzed enantioselective Kinugasa reaction in the synthesis of various chiral *β*-lactams (Scheme 35).[45] When aryl or alkyl-substituted alkynes were employed, the major *cis*-isomer of products

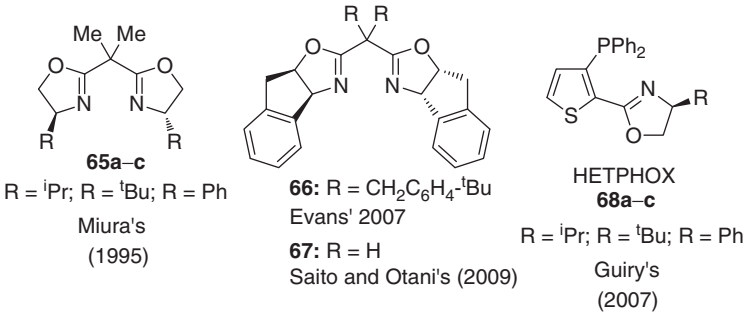
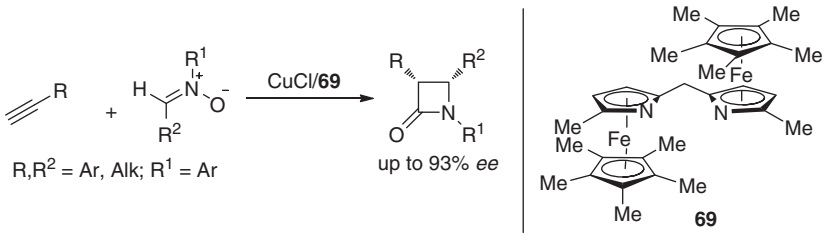
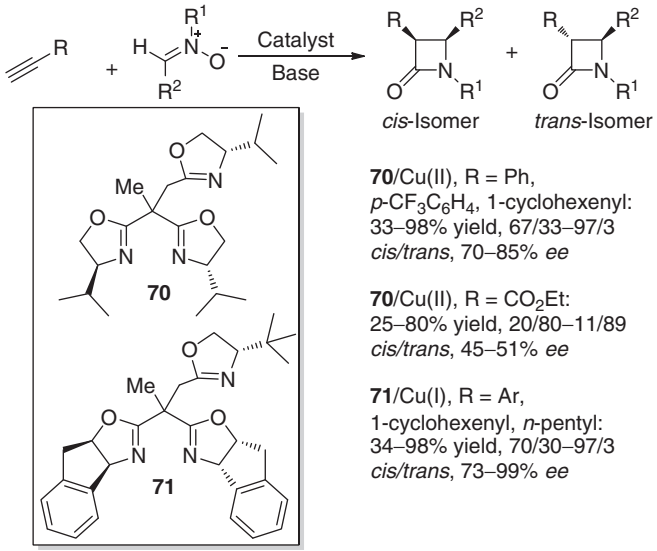


Figure 5 Oxazoline-based ligands used in Kinugasa reactions.



Scheme 34



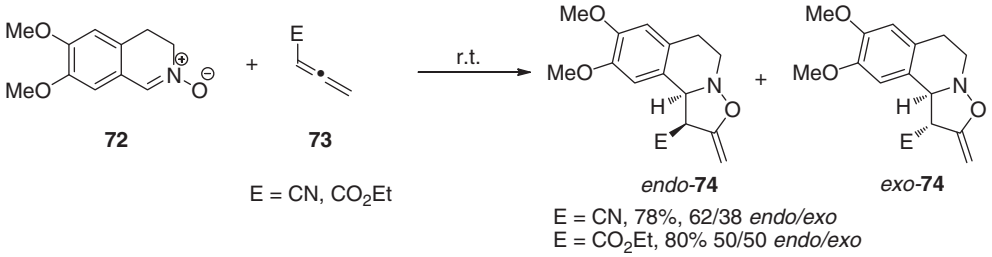
Scheme 35

(67/33–97/3 *cis*/*trans*) were obtained in 33–98% yield with 79–85% *ee*. In contrast, for ester group-substituted alkynes as substrates, the reaction preferred *trans*-selectivity (20/80–11/89 *cis*/*trans*), leading to the corresponding *β*-lactams in 25–80% yield with 45–51% *ee*. Although, copper(II) was employed in this catalytic Kinugasa reaction, it has been proposed that the Cu(II) is reduced *in situ* into Cu(I) by alkyne in the reaction and the catalytic species is still Cu(I). Recently, they have demonstrated another example for the asymmetric Kinugasa reaction in the use of trisoxazoline **71**/copper(I) as catalyst. Good to excellent enantioselectivity (73–99% *ee*) was achieved, and the products were obtained in 34–98% yield with good *cis*-selectivity (70/30–97/3 *cis*/*trans*).[46]

4.22.2.2.2 1,3-Dipolar cycloaddition of nitrones and allenes

Similar to the 1,3-dipolar cycloadditions of nitrones with alkenes, the reaction between nitrones and allenes also takes place regioselectively to afford methylene-substituted isoxazolidine derivatives. As described by Eguchi and coworkers, the *N*-oxide

compound **72** derived from isoquinoline derivatives reacted with electron-withdrawing group-substituted allenes **73** regioselectively, to give diastereomeric mixture of isoxazolines **74** (Scheme 36).[47]

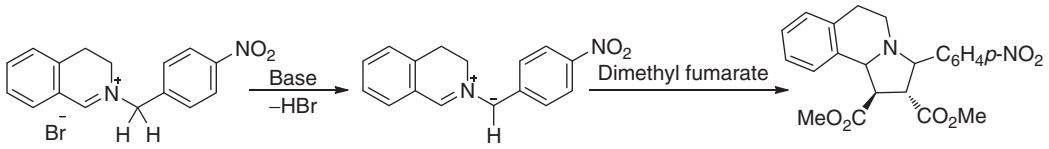


Scheme 36

4.22.3 Azomethine Ylide

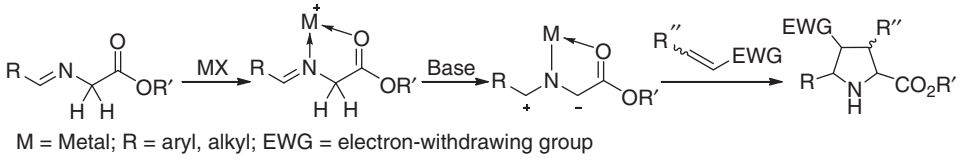
Azomethine ylides are typical 1,3-dipolar compounds, which have the structures of $R_2C{=}N^+R{-}C^-R_2$. The 1,3-dipolar cycloaddition of azomethine ylide with alkenes is an extremely versatile and atom economical process. Many highly efficient and stereoselective methods have been developed for the synthesis of various highly substituted pyrrolidines.[3b,g]

As azomethine ylides were considered as 1,3-dipoles and were investigated in the concepts for 1,3-dipolar cycloaddition reactions in 1963 by Huisgen and coworkers (Scheme 37),[48] successive exploration on this field has been performed to date.



Scheme 37

Although most of the azomethine ylides are unstable, azomethine ylides can be generated from imines of glycine alkyl ester by reaction with a base in the presence of a Lewis acid complex. Stabilized by metal, the azomethine ylide could react with an alkene to give multisubstituted pyrrolidines (Scheme 38).[49a] Zhang et al. recently disclosed an alternative elegant approach for the generation of azomethine ylides from aziridines via C–C bond cleavage, which enables aziridines to participate in a number of [3+2] cycloaddition reactions.[49b–d]

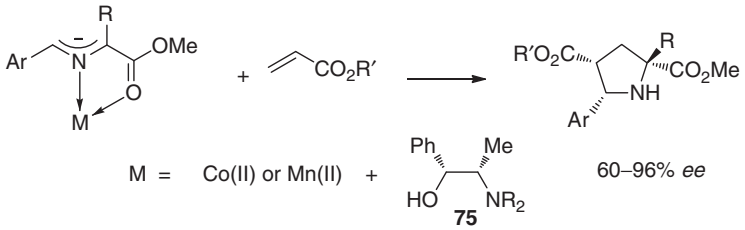


Scheme 38

4.22.3.1 Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with α,β-Unsaturated Carboxylic Derivatives

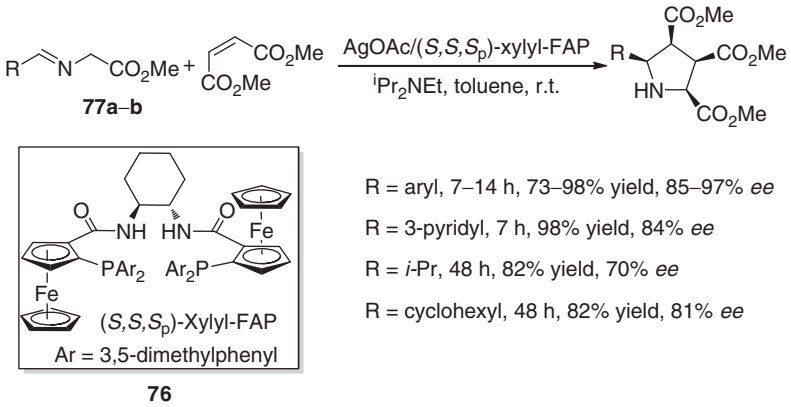
The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with various substituted alkenes provides one of the most direct and efficient pathways for the enantioselective construction of pyrrolidines, and has attracted intensive studies during the past two decades.[3c,e,50] The resulting pyrrolidines are valuable structures that are widely applied in the total synthesis of biologically active natural products, as well as important chiral ligands and building blocks for pharmaceuticals.[3b,51]

Among those studies in this area, most part of the progress was made in the use of transition metal/chiral ligand complex catalysts. Pioneer contribution has been made by Allway and Griggin in 1991. They has reported the 1,3-dipolar cycloaddition reactions of azomethine ylides catalyzed by stoichiometric amounts of chiral complexes formed *in situ* by combination of Co(II) or Mn(II) salts and ephedrine derivatives **75**. The azomethine ylides were generated from imines of glycine methyl ester, and the enantioselective cycloadducts were obtained in 60–96% *ee* (Scheme 39).[52]



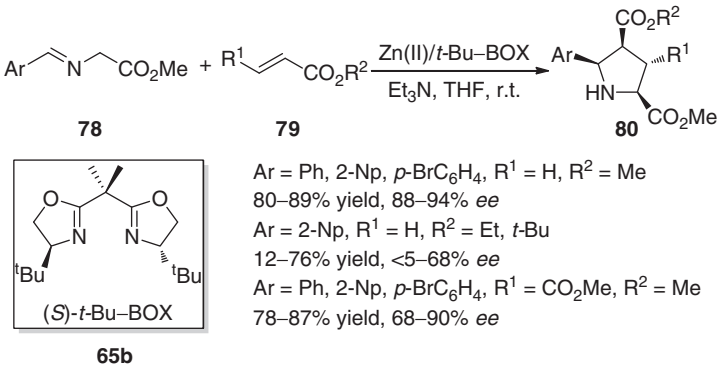
Scheme 39

In 2002, Zhang and coworkers have developed the highly enantioselective Ag(I)-catalyzed [3+2] cycloaddition of azomethine ylides (Scheme 40).[53] A bis-ferrocenyl amide phosphine (FAP) **76** has been successfully employed in this transformation. The ferrocene units of the chiral ligand played an important role in this reaction that the additional element of chirality in the ferrocene units led to excellent enantiocontrol. A number of α-(arylimino)esters **77a** were cyclized in good yield and with high enantioselectivities (up to 97% *ee*), whereas α-(alkylimino)ester substrates **77b**, which are less reactive, produced the corresponding products in lower enantioselectivity (70–81% *ee*).



Scheme 40

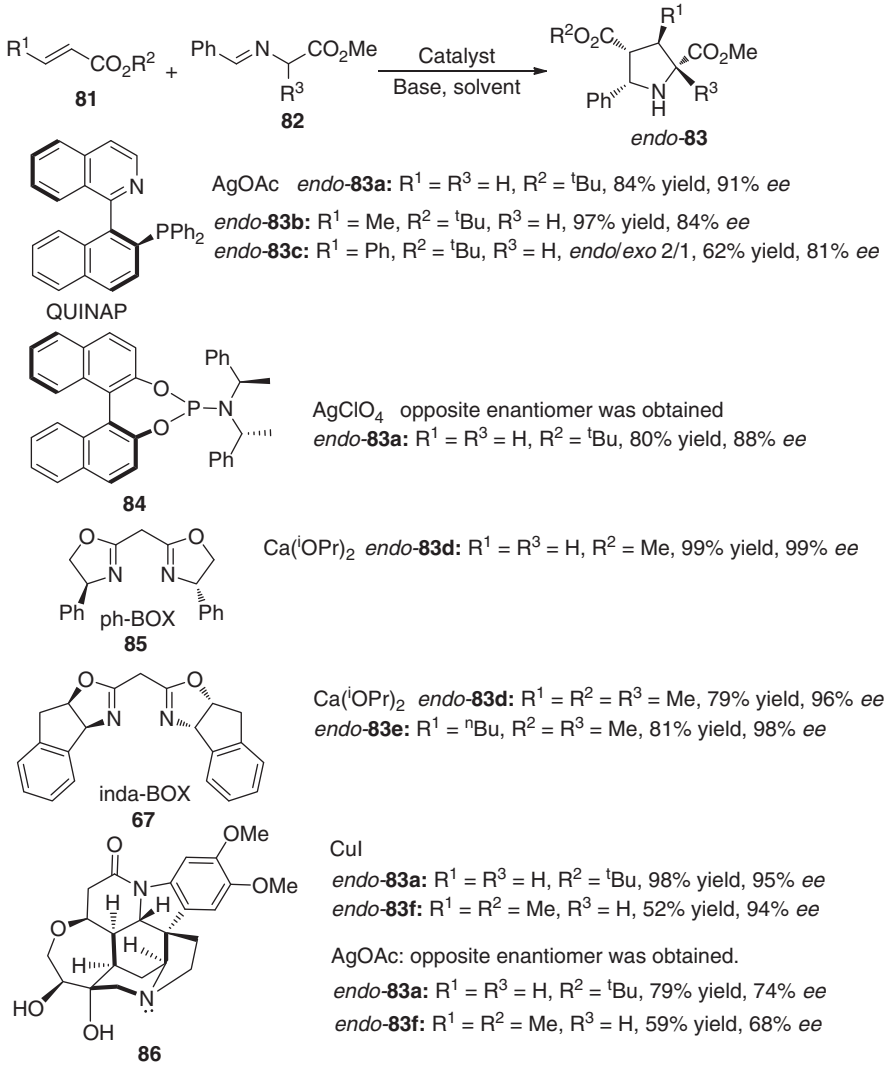
In the same year, Jørgensen and coworkers demonstrated the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides **78** with α,β-unsaturated carboxylic esters **79** catalyzed by zinc(II)/BOX **65b** chiral complex, which provide an easy access to optically active highly functionalized proline derivatives **80** (Scheme 41). In the presence of 10 mol% of catalyst and 10 mol% of Et_3N as base, different *N*-arylmethylidene glycinates reacted with methylacrylate smoothly, to give the cycloadducts in 80–89% yield with up to 94% *ee*. However, ethyl and *tert*-butyl acrylate substrates reacted with *N*-(2-naphthylmethylidene) glycinate gave the pyrrolidines in lower yield with the enantioselectivity dropped to 68% *ee* and <5% *ee*, respectively. Dimethyl fumarate reacted with different azomethine ylides to give the pyrrolidines with four new stereogenic centers in the addition step in good yield with highly diastereo- and enantioselectivities (78–87% yield; 68–90% *ee*).



Scheme 41

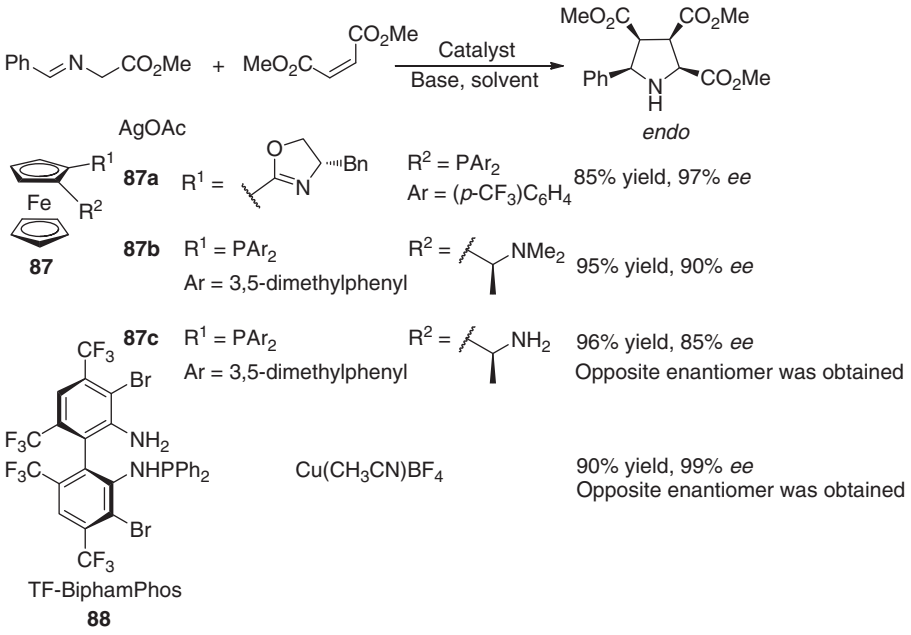
Since then, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide with considerable α,β-unsaturated carboxylic derivatives has been developed using various chiral catalyst systems, such as Cu(I), Cu(II), Ag(I), Ni(II), and Ca(II) complexes of different chiral ligands (e.g., BOX, BINAP, Quinap, and ferrocenyl phosphines), as catalysts.[54]

α,β-Unsaturated carboxylic esters are common candidates in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide (Scheme 42). In 2003, Schreiber and coworkers developed the silver(I) acetate/QUINAP-catalyzed [3+2] azomethine ylide cycloaddition.[54a] Both acrylates **81a** and β-substituted α,β-unsaturated carboxylic eaters **81b–c** reacted smoothly with α-iminoesters **82** derived from aromatic aldehydes, giving the major *endo*-adducts **83** in good yield with up to 91% *ee*. Chiral BINOL-derived phosphoramidite **84**-silver(I) complexes have showed good capability in the 1,3-dipolar cycloaddition of azomethine ylide with *tert*-butyl acrylate **81a**.[54o] Chiral calcium–BOX **85** and **67** complexes as Brønsted base catalysts have been demonstrated in the use of 1,3-dipolar cycloaddition of azomethine ylide by Kobayashi and coworkers, which do not need the addition of external bases in the reaction system.[54l,q] These catalysts effectively promoted the [3+2] cycloaddition in high yield with excellent enantioselectivities. Kim and coworkers have explored brucine-derived amino alcohol **86**-metal complex-catalyzed 1,3-dipolar cycloaddition reactions.[54s] The reversal of enantioselectivity has been investigated between the copper(I)- and silver(I)-complex catalysts.



Scheme 42

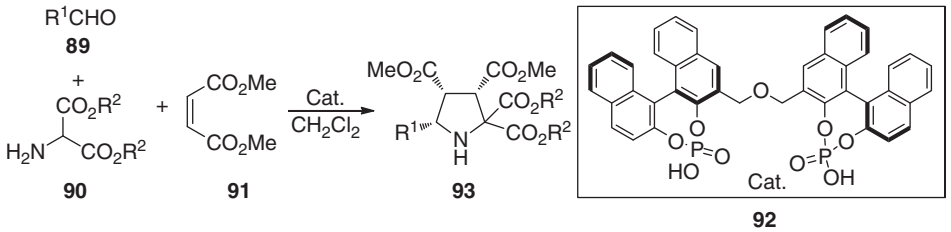
Electron-deficient alkenes such as maleates are widely employed in the asymmetric cycloaddition of azomethine ylides, from which a series of ferrocene-derived N,P ligands **87a–c** have been successfully developed by Zhou and coworkers in the silver(I)-catalyzed transformation (Scheme 43).[54g,n] The AgOAc–ferrocenyloxazoline complex was capable of promoting the [3+2] cycloaddition in good yield with high enantioselectivity.[54g] In addition, the acetate acted as base that deprotonated the α-iminoesters to form the azomethine ylide; thus extra base is not necessary. A hydrogen bonding-directed reversal of



Scheme 43

enantioselectivity was achieved in the AgOAc-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with maleates.[54n] This method provides an efficient approach to both enantiomers of the optically active pyrrolidine derivatives. A novel CuI/TF–BiphamPhos **88** complex is employed in the 1,3-dipolar cycloaddition of azomethine ylides giving the substituted pyrrolidine products in high yield and excellent enantioselectivities.[54r]

Gong and coworkers have described a Brønsted acid-catalyzed three-component asymmetric 1,3-dipolar cycloaddition between aldehydes **89**, amino esters **90**, and dipolarophiles **91** (Scheme 44).[55] A new bisphosphoric acid **92** derived from the linked BINOL has been employed as catalyst, providing polysubstituted pyrrolidines **93** in high yield with excellent enantioselectivities under mild conditions.

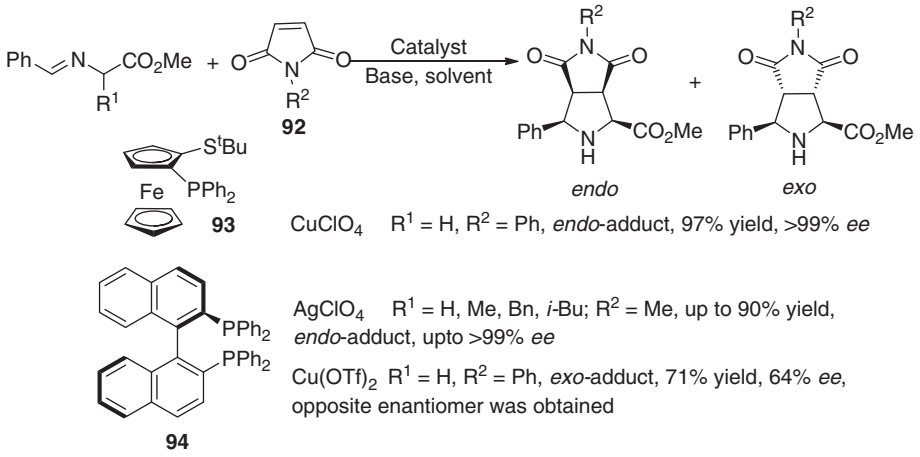


Scheme 44

Maleimides **92** are popular dipolarophiles in the enantioselective 1,3-dipolar cycloaddition of azomethine ylides. Carretero and coworkers have developed the Cu(I)–Fesulphos **93** catalyst system in enantioselective 1,3-dipolar cycloadditions of azomethine ylides, which achieved good to excellent reactivity, *endo*/*exo*-selectivity, and enantioselectivity with broad substrate scope (Scheme 45).[54d] A recyclable chiral Binap **94**–Ag(I) complex catalyst has been described by Nájera, Sansano, and coworkers (Scheme 45).[54k] The reactions are performed at room temperature, in up to 90% yield, with high *endo*-diastereoselectivity and up to >99% *ee*. A series of cycles were run employing the same recovered catalyst which had been recovered by simple filtration. The corresponding cycloadduct was obtained in a slightly decreased yield with almost maintained enantioselectivity. Although the cycloaddition of azomethine ylides catalyzed by Lewis acid complexes usually afforded *endo*-adducts as the predominant product, Komatsu and coworkers have demonstrated the first example of an *exo*-selective cycloaddition, using chiral phosphine–copper complexes as catalysts (Scheme 45).[54b]

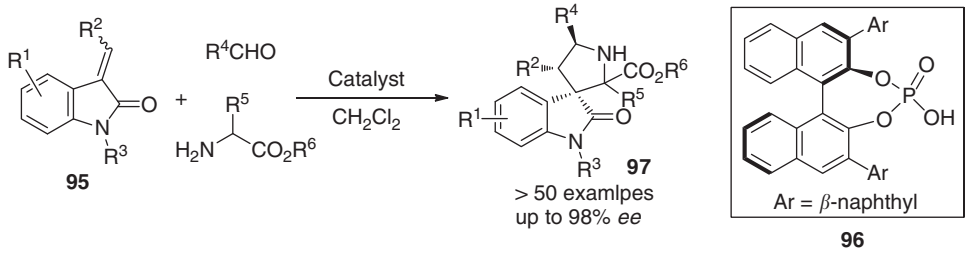
In addition, the axially chiral BINIM–Ni(II) complexes catalyzed the asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides and *N*-aryl maleimides have been reported by Shi and coworkers, which provided the corresponding adducts in good yield with up to 95% *ee*'s.[54p]

In 2009, Gong and coworkers have developed an asymmetric catalytic three-component 1,3-dipolar cycloaddition of a broad range of methyleneindolinones **95** with aldehydes and amino esters in the presence of chiral phosphoric acid **96**, which provide an



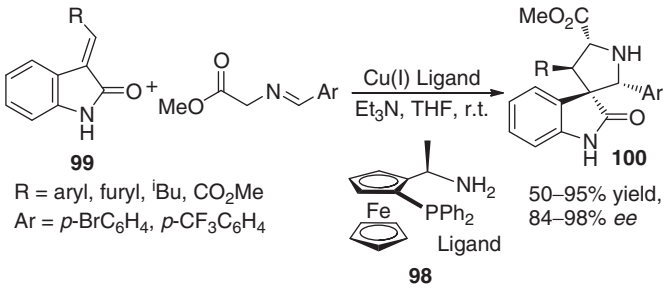
Scheme 45

easy approach to the rapid synthesis of spiro[pyrrolidin-3,3′-oxindole] derivatives **97** in high yield with unusual regiochemistry and excellent stereoselectivities (up to 98% *ee*) under mild conditions (Scheme 46).[56] Theoretical calculations disclosed that the hydrogen bond existed between phosphoric acid and azomethine ylide as well as between methylene indolinone and phosphoric acid.



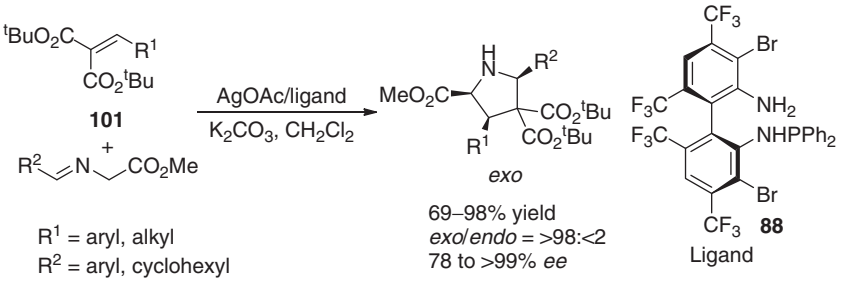
Scheme 46

Catalyzed by Cu(I)–*N*,*P*-ferrocenyl ligand **98** complex, a highly enantioselective synthesis of natural product-inspired 3,3′-pyrrolidinyl spirooxindoles have been reported by Waldmann and coworkers (Scheme 47).[54v] This synthesis takes place by means of asymmetric 1,3-dipolar cycloadditions of azomethine ylide to a series of substituted 3-methylene-2-oxindole **99**, affording cycloadducts **100** in 50–95% yield with 84–98% *ee*.



Scheme 47

Wang and coworkers have developed the *exo*-selective asymmetric 1,3-dipolar cycloaddition of alkylidene malonates **101** with azomethine ylides catalyzed by AgOAc/TF–BiphamPhos (Scheme 48).[54w] Good yield and good to excellent enantio/diastereoselectivities were obtained for a variety of alkenes and azomethine ylide substrates. In addition, this type of chiral ligands have been successfully applied to the 1,3-dipolar cycloaddition of alkylidene cyclopropanes by the same research group.[54x]

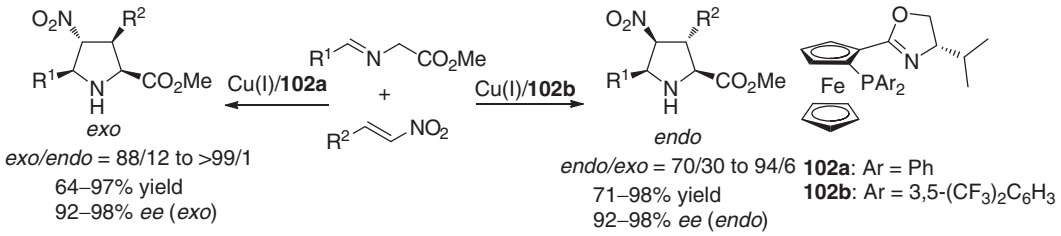


Scheme 48

4.22.3.2 Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Nitroalkenes, Alkenylsulfones, and Enones

The 1,3-dipolar cycloadditions of azomethine ylides with electron-deficient alkenes such as nitroalkenes and alkenylsulfones are very useful transformations for the introduction of versatile nitro- and sulfonyl-functionalized substituents into the pyrrolidine moiety.[54d,57] Cossío and coworkers have demonstrated the mechanism of cycloaddition of nitroalkenes with azomethine ylides in both theoretical and experimental ways. In the case of the Lewis acid activated reactions generated *N*-metalated azomethine ylides, the reaction proceeds via the stepwise mechanism.[57a,b]

In 2005, Carretero and coworkers have reported one example of the catalytic asymmetric 1,3-dipolar cycloaddition of *β*-nitrostyrene with *N*-benzylidene methyl glycinate.[54d] The first general protocol of this reaction has been demonstrated by Hou and coworkers (Scheme 49).[57c] In this CuI-catalyzed asymmetric 1,3-dipolar cycloaddition, electronic properties of the ligands switch the diastereoselectivity. *exo*- or *endo*-Pyrrolidines were obtained with high diastereo- (up to >99/1 *exo*/*endo*; up to 94/6 *endo*/*exo*) and enantioselectivities (92–98% *ee*) by using electron-rich or -deficient aryl groups on the P atom of chiral *P*,*N*-ferrocene ligands **102a**,**b**, respectively.

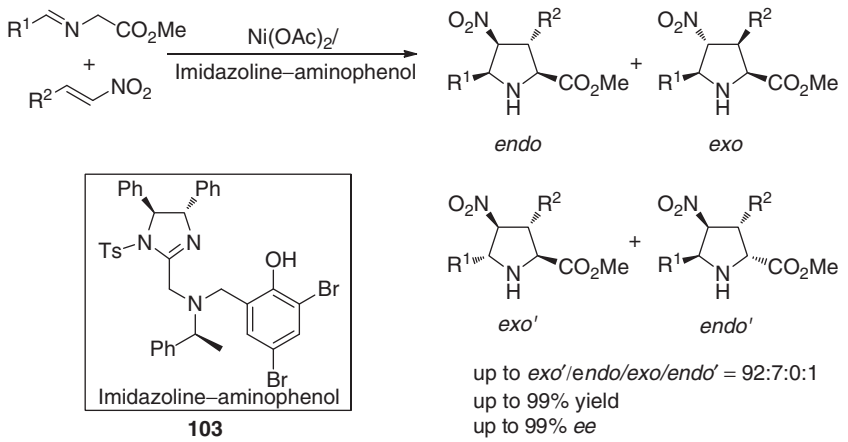


Scheme 49

The cycloaddition of azomethine ylides with nitroalkenes to afford the pyrrolidine ring could generate four stereogenic centers and up to eight diastereomers. When a *trans*-nitroalkene is used, the stereoconjunction between the 3- and 4-positions is fixed in a *trans*-conformation. There could be four possible diastereomers, classified as *endo*-, *exo*-, *endo*′-, and *exo*′- isomers. Recently, Arai and coworkers have reported the first successful catalytic asymmetric *exo*′-selective reaction of iminoesters and nitroalkenes (Scheme 50).[57e] This unusual control of the stereoselectivity was made by employing a chiral imidazoline–aminophenol **103**/Ni $(OAc)_2$ complex. DFT study suggests that the *exo*′ adduct is the most stable one among the four possible isomers. Thermodynamic control over the stepwise Michael/Mannich cyclization steps gives the adducts in up to 99% *ee*. In addition, they have also succeeded in the development of a new bis(imidazolidine)pyridine–Cu complex for the highly *endo*-selective 1,3-dipolar cycloaddition of iminoesters to trisubstituted nitroalkenes.[57d]

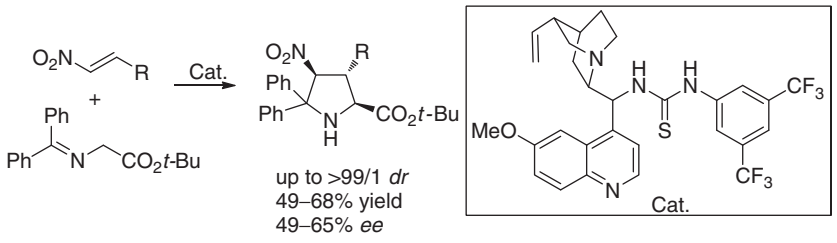
In 2008, Gong and coworkers have discovered the first organocatalytic stereoselective 1,3-dipolar cycloaddition of azomethine ylide with nitroalkenes in good yield and stereoselectivities, in particular with up to >99/1 diastereoselectivities (Scheme 51).[58] This method provides a direct access to the optical active highly substituted pyrrolidines. They have also demonstrated the asymmetric 1,3-dipolar cycloaddition reaction of *α*-substituted isocyanoesters with nitroolefins catalyzed by *Cinchona* alkaloid derivatives to yield 2,3-dihydropyrroles with excellent diastereo- and enantioselectivities.[59]

Chen and coworkers have described a monothiourea compound **104** catalyzed 1,3-dipolar cycloaddition via a one-pot, three-component reaction of aldehydes, diethyl *α*-aminomalonate and nitroalkenes with high enantioselectivities (Scheme 52).[60]



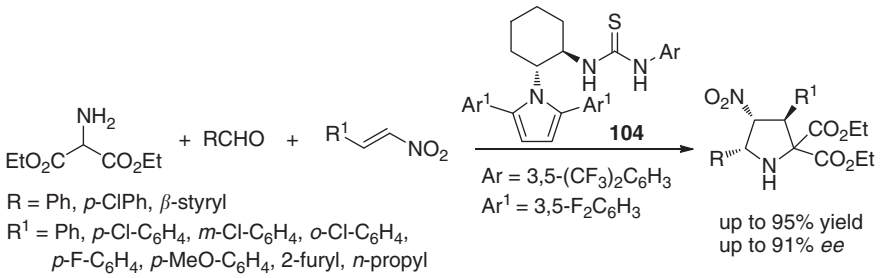
R^1 = Ph, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-ClC_6H_4, 3,4-(OCH_2O)-C_6H_3, 1-naphthyl, 2-naphthyl
R^2 = Ph, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *m*-ClC_6H_4, *o*-BrC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, 3,4-(OCH_2O)-C_6H_3, $CH_3(CH_2)_4$, $Ph(CH_2)_2$

Scheme 50



R = Ph, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *o*-MeC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-FC_6H_4, 2-thienyl

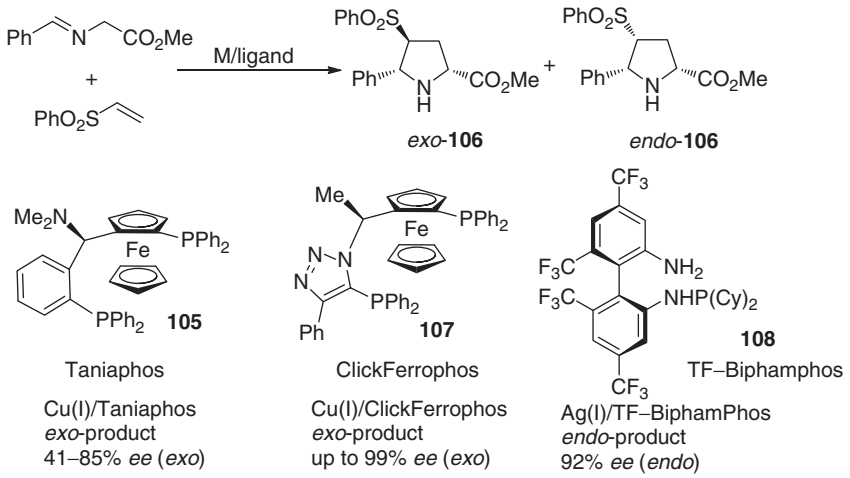
Scheme 51



R = Ph, *p*-ClPh, *β*-styryl
R^1 = Ph, *p*-Cl-C_6H_4, *m*-Cl-C_6H_4, *o*-Cl-C_6H_4, *p*-F-C_6H_4, *p*-MeO-C_6H_4, 2-furyl, *n*-propyl

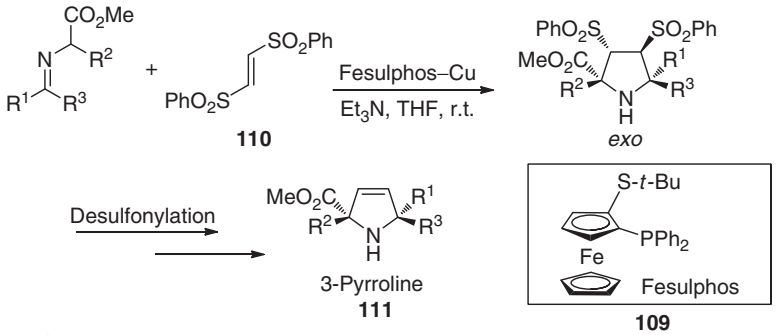
Scheme 52

The pioneering study on the asymmetric 1,3-dipolar cycloaddition of phenyl vinyl sulfone with azomethine ylides was carried out by Grigg and coworkers in the presence of stoichiometric amounts of AgOTf and a chiral *P,P*-ligand.[52b] The first general protocol for the catalytic enantioselective reaction has been developed by Carretero and coworkers (Scheme 53).[61] The CuI–Taniaphos **105** catalyst has been used, providing 3-sulfonyl pyrrolidines **106** with very high *exo*- and enantioselectivities in the range 41–85% *ee*. Fukuzawa and coworkers have also demonstrated the same transformation employing Cu(I)/ClickFerrophos **107** complex as catalyst.[62] The *exo*-**106** isomers were produced predominantly, with high enantioselectivity (up to 99% *ee*) (Scheme 53). In 2009, Wang and coworkers have reported the first catalytic *endo*-selective 1,3-dipolar cycloaddition of azomethine ylides and phenyl vinyl sulfone.[63] The highly efficient AgOAc/TF-BiphamPhos **108** catalytic system showed the best performance; excellent diastereoselectivity (>98/2) and good enantioselectivity (67–92% *ee*) have been achieved in broad substrate scope under mild conditions (Scheme 53).



Scheme 53

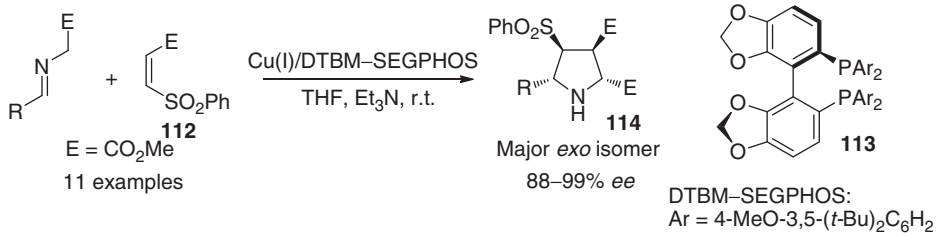
The highly enantioselective Fesulphos **109**-Cu catalyzed 1,3-dipolar cycloaddition of azomethine ylides with *trans*-1,2-bisphenyl sulfonylethylene **110** has been developed by Carretero and coworkers.[64] Followed by reductive desulfonylation, this methodology provides a practical approach to the asymmetric synthesis of 3-pyrrolines **111** (Scheme 54). In addition, Nájera and coworkers have demonstrated that Binap–silver[65]and Binap–gold[66] trifluoroacetate complexes are also effective catalysts for this reaction, giving the *endo*-adducts with high enantioselectivity.



R^1 = *p*-$MeOC_6H_4$, *m*-MeC_6H_4, *m*-FC_6H_4, *o*-MeC_6H_4, *p*-N-$(Boc)_2$-C_6H_4, 2-naphtyl, 2-furyl, CH=CH-Ph, Cy, *t*-Bu
R^2 = H, Me
R^3 = H, Me, Ph

Scheme 54

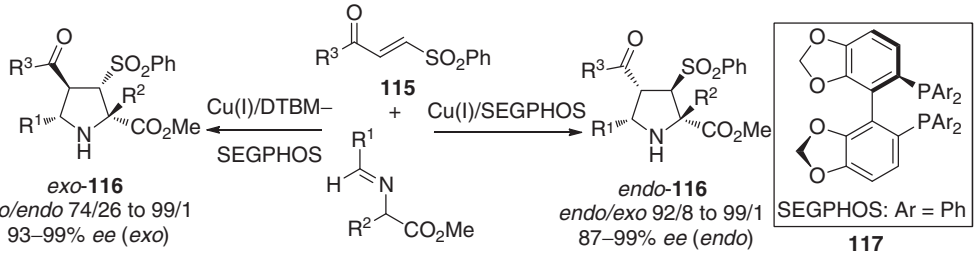
Recently, Carretero and coworkers have developed a general procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of (*Z*)-sulfonyl acrylates **112** with azomethine ylides (Scheme 55).[67] Using CuI/DTBM–SEGPHOS **113** as the catalyst system, the reaction provides 2,3-dicarboxylate-substituted pyrrolidines **114** with high *exo*-selectivity and good to excellent enantioselectivity (80–99% *ee*). The regioselectivity of the cycloaddition is mainly controlled by the sulfonyl group.



R = *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *m*-FC_6H_4, *o*-MeC_6H_4, *p*-N-$(Boc)_2$-C_6H_4, 2-naphtyl, 2-thienyl, 2-pyrryl, CH=CH-Ph, Cy

Scheme 55

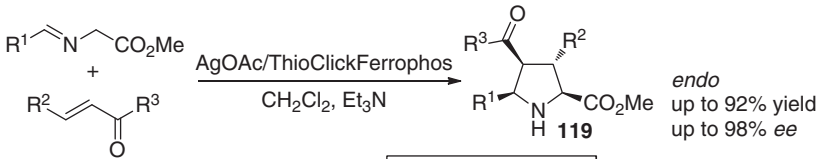
They have also reported a catalytic asymmetric 1,3-dipolar cycloaddition using (*E*)-*β*-phenylsulfonyl enones **115** as dipolarophiles to provide highly functionalized pyrrolidine derivatives **116** (Scheme 56).[68] In the presence of chiral CuI–SEGPHOS catalysts, the adducts were obtained with high regio-, diastereo-, and enantioselectivities. Interestingly, the *endo*/*exo*-selectivity of this procedure is controlled by the aryl groups on the P atom of chiral ligands, as those from *endo*- to *exo*-selectivity were observed when SEGPHOS **117** or DTBM–SEGPHOS **113** ligand was used.



R^1 = Ph, *m*-MeC_6H_4, *o*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-BrC_6H_4, naphtyl, thienyl; R^2 = H, Me; R^3 = Me, *i*-Pr

Scheme 56

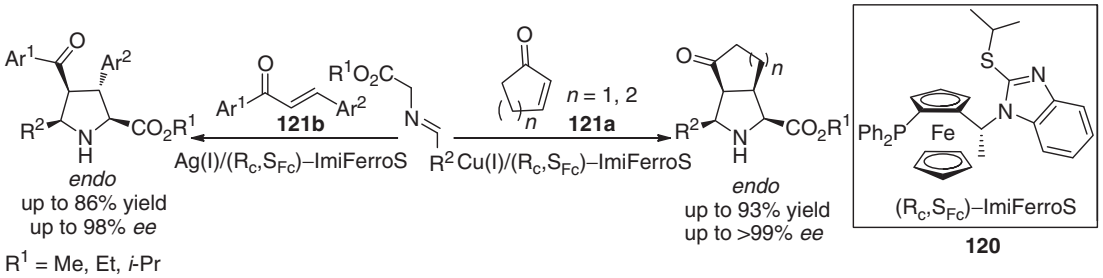
In 2010, Fukuzawa and coworkers have demonstrated the Ag(I)/ThioClickFerrophos **118** catalyzed *endo*-selective asymmetric 1,3-dipolar cycloaddition of azomethine ylide with (*E*)-acyclic and cyclic enones (Scheme 57).[69] The *endo*-4-acyl-substituted pyrrolidines **119** can be obtained in good yield with high *endo*/*exo*-selectivities and enantioselectivities (up to 98% *ee*).



R^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$MeOC_6H_4$, 2-naphthyl, Cy
R^2 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-$CF_3C_6H_4$, 2-naphthyl, Me
R^3 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, 2-naphthyl, Me, CH=CHPh

Scheme 57

A new family of chiral ferrocenyl P,S-ligands ((R_c,S_{Fc})–ImiFerroS **120**) has been developed by Hu and coworkers, and has been successfully applied in a highly *endo*-selective catalytic asymmetric cycloaddition of azomethine ylides with various enones (Scheme 58).[70] For cyclic *α*-enones **121a**, a copper(I) complex catalyzed the cycloaddition to give the *endo*-cycloadducts

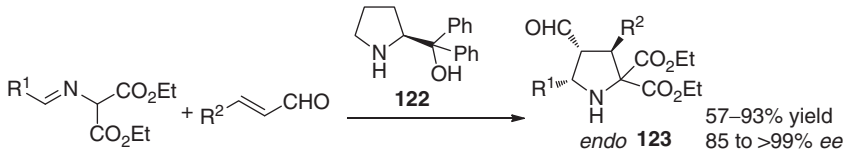


R^1 = Me, Et, *i*-Pr
R^2 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl, 2-naphthyl, Cy, et al.
Ar^1 = Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *p*-MeC_6H_4
Ar^2 = Ph, *p*-ClC_6H_4

Scheme 58

exclusively in excellent enantioselectivities (normally 99% *ee*), whereas for acyclic enones **121b**, a silver(I)/ligand catalytic system exhibited good *endo*/*exo*-selectivities (*endo*/*exo* = 91/9 to 96/4) and high enantiocontrol (up to 98% *ee*).

In addition, organocatalysts have also shown its promising ability in the enantiocontrol of catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with α,β-unsaturated aldehydes in recent years.[71] In 2007, Vicario and coworkers have described the first organocatalytic enantioselective [3+2] cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides (Scheme 59).[71b] In the presence of commercially available α,α-diphenylprolinol **122** as catalyst, the reaction produce the highly functionalized polysubstituted pyrrolidines **123** as single regioisomers in excellent yield with excellent diastereo- and enantioselectivities. Córdova and coworkers have reported the three-component involved L-prolinol derivatives catalyzed 1,3-dipolar cycloaddition among aldehydes, dialkyl 2-aminomalonates, and α,β-unsaturated aldehydes.[71a] The reaction gives access to multifunctionalized pyrrolidine derivatives in good yield with high diastereoselectivities (>10:1 *dr*) and 90–98% *ee*.

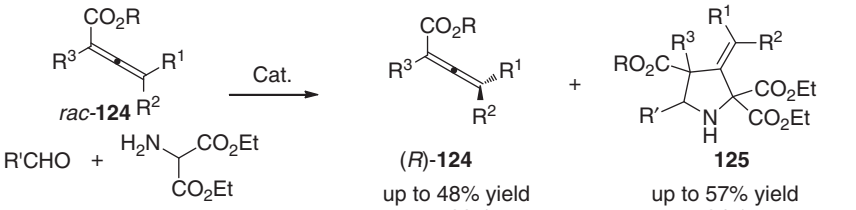


R^1 = Ph, *p*-$MeOC_6H_4$, (3,4-OCH_2O)C_6H_3, 3,5-$(MeO)_2C_6H_3$, *o*-$MeOC_6H_4$, *p*-FC_6H_4, *o*-FC_6H_4, *o*-tolyl, 2-furyl, (*E*)-CH_3CH=CH
R^2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, Ph, *p*-$NO_2C_6H_4$, *p*-$MeOC_6H_4$, 2-furyl

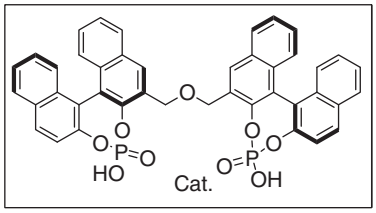
Scheme 59

4.22.3.3 Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Allenes

In 2009, Gong and coworkers have developed a bisphosphoric acid **92**-catalyzed 1,3-dipolar cycloaddition of buta-2,3-dienoates with azomethine ylides, furnishing the 3-methylenepyrrolidine derivatives with excellent enantioselectivity (up to 97% *ee*).[72] By using the same catalyst, they have also realized the kinetic resolution of racemic 2,3-allenoates **124** via the same reaction, affording the optically active 2,3-allenoates (*R*)-**124** and 3-methylenepyrrolidine derivatives **125** in high yield and enantioselectivities (Scheme 60).[73]



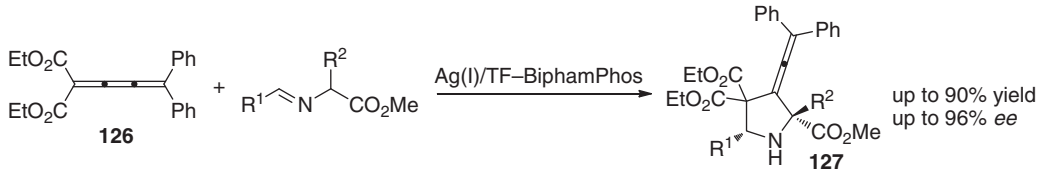
R^1 = Et, Bn, $Cl(CH_2)_2$
R^2 = Bn, Me, allyl, H, CH_2CO_2Bn, 4-$BrC_6H_4CH_2$
R^3 = 9-anthracenylmethyl
R′ = 4-BrC_6H_4



92

Scheme 60

Recently, Wang and coworkers have demonstrated a catalytic asymmetric 1,3-dipolar cycloaddition of various azomethine ylides with diethyl 2-(3,3-diphenylpropa-1,2-dienylidene)malonate **126**, aiming for an efficient construction of 3-vinylidenepyrrolidine derivatives **127** bearing an allene moiety (Scheme 61).[74] The reaction was promoted by an Ag(I)/TF–BiphamPhos **88** complex as catalyst. Good to excellent enantioselectivity has been achieved.



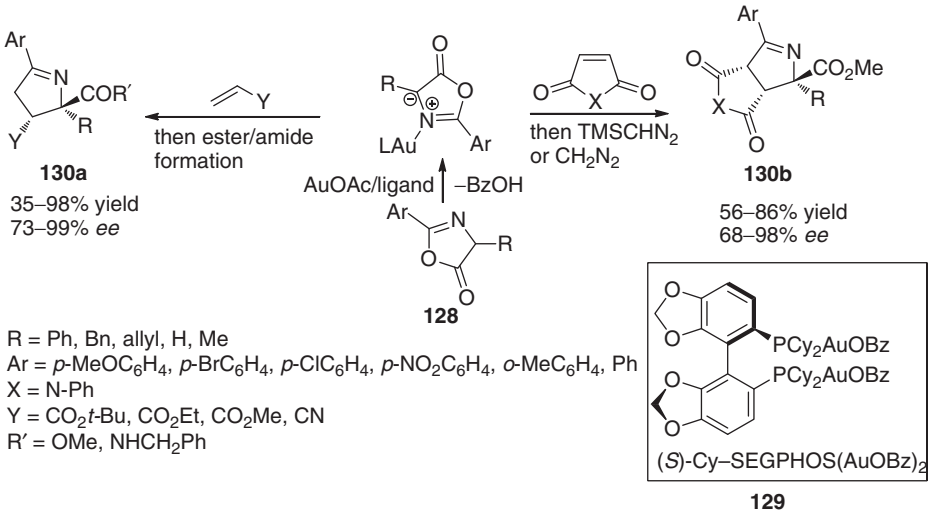
R^1 = Ph, *p*-MeC_6H_4, *m*-MeC_6H_4, *p*-ClC_6H_4, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CF_3C_6H_4$, 2-naphthyl, 2-furyl, Bn, cyclohexyl

R^2 = H, Me, Ph

Scheme 61

4.22.3.4 Catalytic Asymmetric 1,3-Dipolar Cycloadditions from Other Azomethine Ylide Precursors

The 1,3-dipolar cycloaddition of münchnone dipoles is proposed to proceed through a 1,3-dipole generated by deprotonation of a metal-activated azlactone **128**. In 2007, the first catalytic enantioselective example has been described by Toste and coworkers (Scheme 62).[75] The reaction is catalyzed by chiral bis(phosphine)gold(I) benzoate complexes **129**, and process smoothly with various electron-deficient alkenes, affording Δ1-pyrrolines **130a**,**b** with good to excellent regio-, diastereo-, and enantioselectivities.



R = Ph, Bn, allyl, H, Me

Ar = *p*-$MeOC_6H_4$, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *o*-MeC_6H_4, Ph

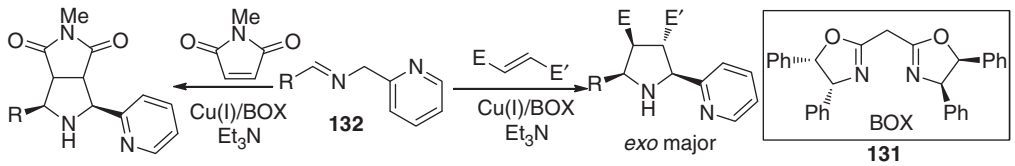
X = N-Ph

Y = CO_2t-Bu, CO_2Et, CO_2Me, CN

R′ = OMe, $NHCH_2Ph$

Scheme 62

In 2010, Adrio and coworkers have developed an efficient Cu(I)/BOX **131**-catalyzed asymmetric 1,3-dipolar cycloaddition of *N*-(2-pyridylmethyl) imines **132** (Scheme 63).[76] Good to excellent enantioselectivity (up to 97% *ee*) and moderate to high *exo*-selectivity were achieved with a wide variety of substituted dipolarophiles, including maleimides, fumarates, fumarodinitrile, enones, and nitroalkenes. In addition, they have also reported a catalytic asymmetric 1,3-dipolar cycloaddition involving α-iminonitriles as azomethine precursors.[77]



17 examples, 45–90% yield, 68–97% *ee*

R = *p*-$OMeC_6H_4$, *m*-MeC_6H_4, *p*-BrC_6H_4, *o*-FC_6H_4, *p*-$NO_2C_6H_4$, 2-thienyl, 2-furyl, 2-pyridyl, Ph-CH=CH, Cy

E, E′ = CO_2Me, COPh, CN, NO_2, Ph

Scheme 63

The first catalytic asymmetric 1,3-dipolar cycloadditions of Schiff bases of α-aminophosphonates **133** with olefins have been described by Kobayashi and coworkers (Scheme 64).[78] The reaction is catalyzed by chiral silver amide complexes bearing

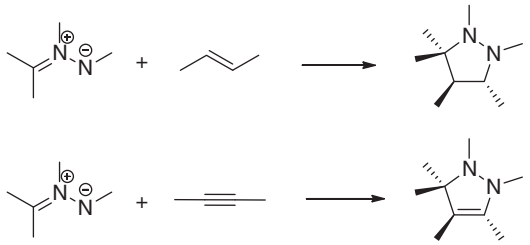
R^1 = Ph, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-FC_6H_4, *p*-$CF_3C_6H_4$, 3-pyridyl, 1-naphthyl, 2-naphthyl, cinnamyl, *i*-Pr
R^2 = H, Me
R^3 = CO_2*t*-Bu, CO_2Et, $CONMe_2$, COMe, SO_2Ph, $PO(OEt)_2$, CN

Scheme 64

(*R*)-DTBM–SEGPHOS **113**, and proline phosphonic analogs **134** were obtained in high yield with excellent diastereo- and enantioselectivities.

4.22.4 Azomethine Imines

The 1,3-dipolar cycloaddition of azomethine imines with alkenes or alkynes leads to the formation of pyrazolines or 1*H*-pyrazole, respectively (Scheme 65).



Scheme 65

With regard to the azomethine imines as 1,3-dipole, acyclic azomethine imines **I** preferentially exist as a hemiaminal form **II**, which are inappropriate in asymmetric catalysis.[79] *N,N′*-cyclic azomethine imines **III** has been employed widely in the asymmetric 1,3-dipolar cycloadditions.[80] Recently, *C,N*-cyclic azomethine imines **IV** have been developed as another type of azomethine imines, and their property and synthetic utility have been documented (Figure 6).[81]

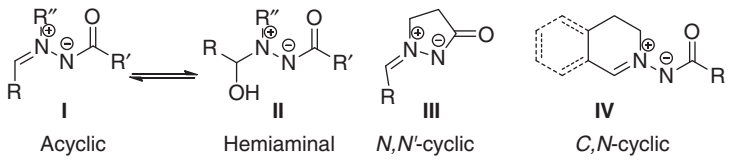


Figure 6 Classification of azomethine imines.

As a relevant strategy, hydrazones have been used as acyclic azomethine imine analogs in the asymmetric 1,3-dipolar cycloadditions with olefins (Figure 7).[82]

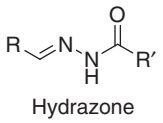
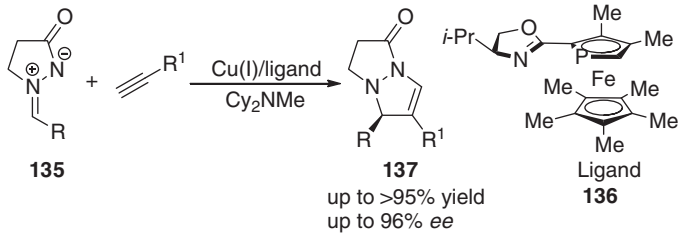


Figure 7 An acyclic azomethine imine analog.

4.22.4.1 Catalytic Asymmetric 1,3-Dipolar Cycloadditions of Cyclic Azomethine Imines with Alkenes and Alkynes

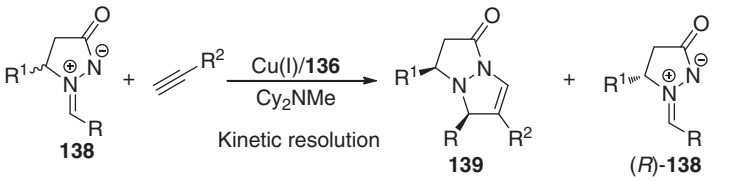
In 2003, Fu and coworkers have developed a new copper-catalyzed 1,3-dipolar cycloaddition of *N*,*N*′-cyclic azomethine imines **135** and terminal alkynes (Scheme 66).[80a] By employing a phosphaferrocene oxazoline **136** as a chiral bidentate ligand, a wide range of azomethine imines and alkynes are tolerated, furnishing useful heterocycles **137** in very good *ee*. In this reaction, the copper is likely to generate a transient formation of a copper acetylide to enhance the reactivity of the dipolarophile.



R = Ph, *o*-FC_6H_4, *m*-BrC_6H_4, *p*-$CF_3C_6H_4$, 1-cyclohexenyl, *n*-pentyl, Cy
R^1 = CO_2Et, COMe, CONMePh, *p*-$EtO_2CC_6H_4$, *p*-$CF_3C_6H_4$, 2-pyridyl, Ph, *n*-pentyl

Scheme 66

In 2005, they have also described an effective method for the kinetic resolution of racemic azomethine imines **138** via 1,3-dipolar cycloadditions catalyzed by chiral copper complex, providing a wide array of useful enantioenriched azomethine imines (*R*)-**138**, which can readily be transformed into monocyclic and bicyclic pyrazolidinones **139** (Scheme 67).[80b]



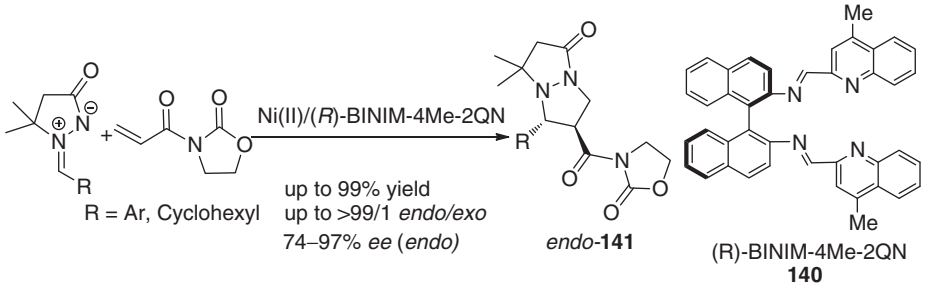
R^1 = Ph, *m*-BrC_6H_4, 2-thienyl, *i*-Pr, *t*-Bu
R^2 = CO_2Et, CONMePh

31–48% yields
91–99% *ee*

R = Ph, Cy,

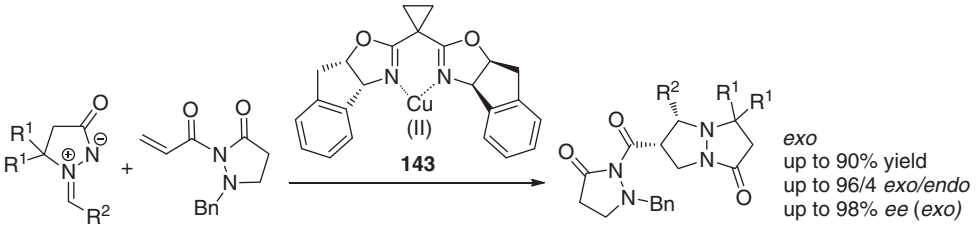
Scheme 67

The first highly enantioselective metal-catalyzed 1,3-dipolar cycloaddition reactions between cyclic azomethine imines and electron-deficient alkenes has been developed by Suga and coworkers (Scheme 68).[80e] By employing chiral BINIM**140**–Ni(II) complex as a chiral Lewis acid catalyst, the cycloaddition is dipole-HOMO/dipolarophile-LUMO controlled, furnishing cycloadducts **141** in up to 99% yield with 74–97% *ee* and high *endo*-selectivity (>99:1–64:36).



Scheme 68

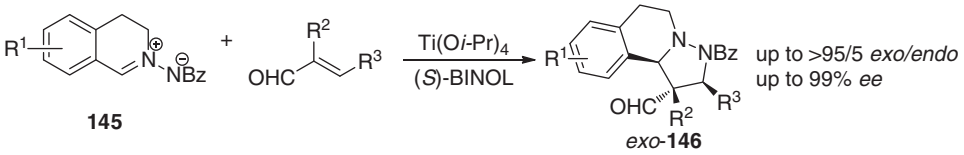
Sibi and coworkers have demonstrated a strategy for *exo*-selective enantioselective 1,3-dipolar cycloaddition of azomethine imines to 2-acryloyl-3-pyrazolidinone **142**. In the presence of copper(II)/IndaBOX complex **143** as catalyst, the corresponding cycloadducts **144** are obtained in up to 90% yield with high diastereoselectivities (up to >96:4 *exo*/*endo*) and enantioselectivities (up to 98% *ee*) (Scheme 69).[80g]



R^1 = Me, H, Et, $-(CH_2)_5-$
R^2 = Ph, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-CNC_6H_4, *o*-ClC_6H_4, *o*-FC_6H_4, *i*-Pr

Scheme 69

Maruoka and coworkers have successfully demonstrated another type of *C,N*-cyclic azomethine imine **145**, and have utilized them as a promising 1,3-dipole in asymmetric 1,3-dipolar cycloadditions (Scheme 70).[81] With titanium–BINOLate as catalyst, the *C,N*-cyclic azomethine imines coupled with enals to give pharmaceutically attractive tetrahydroisoquinoline and piperidine motifs **146** with up to 99% *ee* mainly in *exo*-selectivity.



R^1 = Me, MeO, Br, H; R^2 = Me, H, $-(CH_2)_3-$; R^3 = Me, Pr, Ph, $-(CH_2)_3-$, H

Scheme 70

Interestingly, in the case of *α,β*-unsaturated aldehydes lacking *α,β*-substituent, the reaction was controlled in *endo*-selectivity for the azomethine imines which are not fused to an aromatic ring (up to 93/7 *endo/exo*, up to 97% *ee* for the *endo*-isomer) (Figure 8).

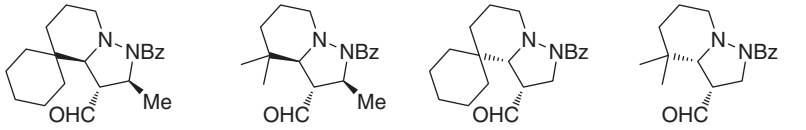
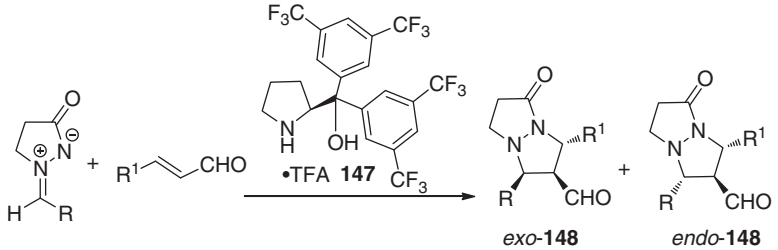


Figure 8 *exo*/*endo*-Selectivities for different *α,β*-unsaturated adehyde substrates.

Organocatalysis has also showed good performance in the field of azomethine imines involved 1,3-dipolar cycloadditions. In 2006, Chen and coworkers have presented the first stereoselective 1,3-dipolar cycloadditions of azomethine imines with *α,β*-unsaturated aldehydes catalyzed by readily available *α,α*-diarylprolinol salts **147** (Scheme 71).[80c] The organocatalyst with strongly

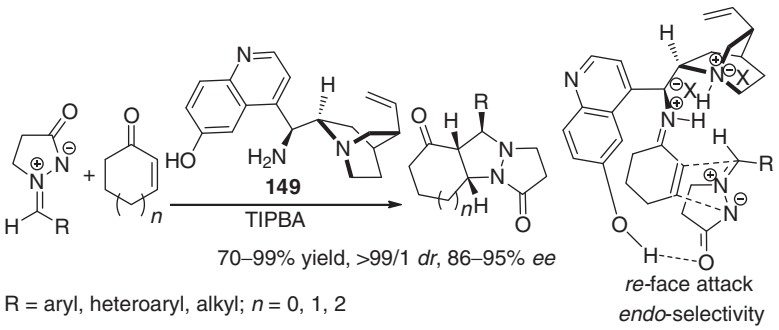


R = Ph, *p*-ClC_6H_4, *p*-FC_6H_4, *p*-$MeOC_6H_4$, *n*-Pr
R^1 = Me, *n*-Pr, *n*-Bu, *i*-Pr

Scheme 71

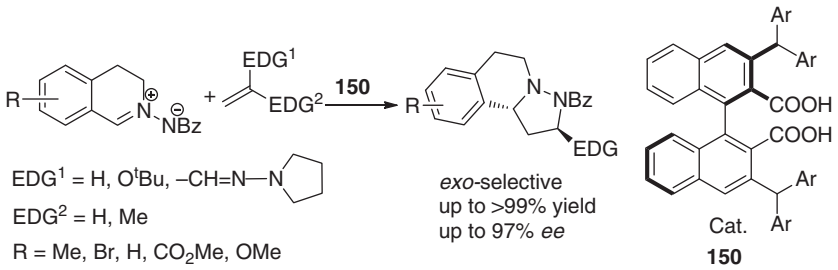
electron-withdrawing groups exhibited high stereoselectivity and catalytic activity in the cycloaddtion reactions, giving the bipyrazolidin-3-one derivatives **148** under mild conditions with 81/19 to 98/2 *exo*/*endo* and 77–97% *ee* for the *exo*-isomer.

In 2007, they have also developed the first organocatalytic and asymmetric 1,3-dipolar cycloaddition of cyclic enones and azomethine imines (Scheme 72).[80d] *Cinchona* alkaloids derived primary amine **149** bearing a synergistic hydrogen-bonding donor has been used as catalyst. The hydrogen-bonding interaction between the hydroxyl group of the catalyst and 1,3-dipole is essential for enantiocontrol, and excellent stereoselectivities were achieved for a broad scope of substrates ($dr > 99{:}1$, up to 95% *ee*).



Scheme 72

Maruoka and coworkers have developed an asymmetric inverse-electron-demand (IED) 1,3-dipolar cycloaddition of *C*,*N*-cyclic azomethine imines and electron-rich alkenes (Scheme 73).[83] A newly developed axially chiral dicarboxylic acid **150** has been employed as catalyst. Using vinyl ethers and vinylogous aza-enamines as dipolarophiles, the concept of IED umpolung 1,3-dipolar cycloaddition was introduced.



Scheme 73

In 2008, Charette and coworkers reported the cycloaddition of 1,1-cyclopropane diesters with quinoline azomethine imines, which developed a useful approach to synthesize racemic 1,2-dihydroquinoline derivatives in up to 87% yield with *dr* up to 6.6/1.[84]

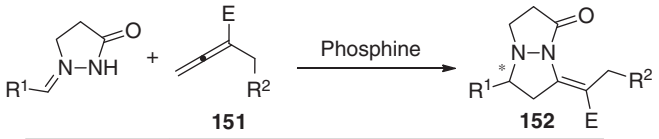
4.22.4.2 Catalytic 1,3-Dipolar Cycloadditions of Cyclic Azomethine Imines with Allenes

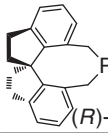
In 2011, Guo et al. have described the phosphine-catalyzed 1,3-dipolar cycloaddition of azomethine imines and allenoates **151**, which marks the first application of nucleophilic phosphine catalysis upon azomethine imines (Scheme 74).[85] The reaction proceeds smoothly under mild reaction conditions, furnishing a broad range of 1,2-dinitrogen-containing heterocycles **152** in moderate to excellent yield. In the use of enantioenriched chiral phosphines **153**, the asymmetric version of this reaction has been realized, giving the corresponding cycloadduct in 56% yield with 89% *ee*.

4.22.4.3 Catalytic Asymmetric 1,3-Dipolar Cycloadditions of Acyclic Hydrazones with Alkenes and Alkynes

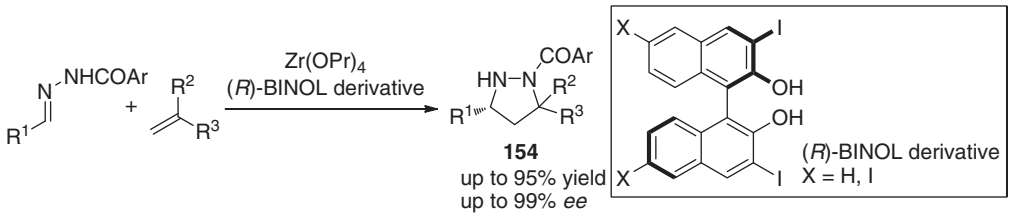
The first example of catalytic asymmetric [3+2] cycloaddition of hydrazones to electron-rich olefins has been demonstrated by Kobayashi and coworkers (Scheme 75).[82a,b] The reactions conducted in high yield with high enantioselectivities using a chiral zirconium catalyst, which provide easy access to synthetically and biologically important pyrazoline, pyrazolidine **154**, and 1,3-diamine derivatives. Several control experiments suggested that the reactions proceeded via concerted pathways.

In the current 1,3-dipolar cycloaddition of hydrazones with olefins, two reaction mechanisms are proposed (Scheme 76). One is a stepwise pathway, nucleophilic addition to the imine moiety and successive cyclization, and the other is a [3+2] concerted pathway, simultaneous cyclization of a 1,3-dipole equivalent with an olefin. In this reaction both diastereomers of the products



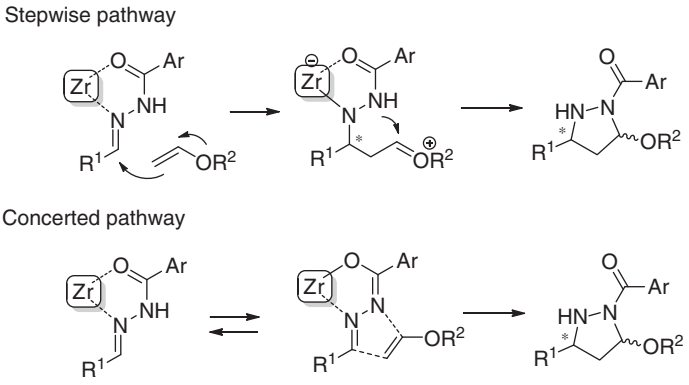
	R^1	R^2	Yield	*ee*
PBu_3	aryl, heteroaryl	H	up to 99%	–
PMe_3	*p*-$NO_2C_6H_4$	alkyl, aryl	up to 99%	–
 (*R*)-**153**	Ph	H	56%	89%

Scheme 74



R^1 = $PhCH_2CH_2$, $(CH_3)_2CHCH_2$, *c*-Hex, $CH_3(CH_2)_4$, Bn, Ph
R^2 = OEt, OPr, O*t*-Bu, SEt; R^3 = H, SEt

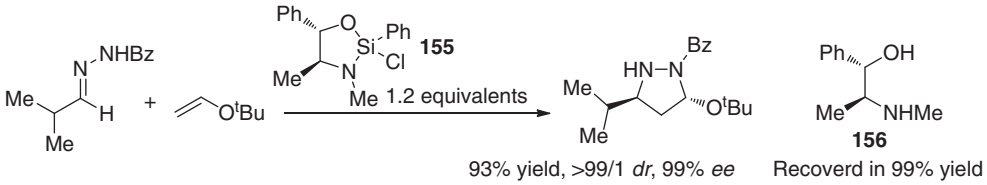
Scheme 75



Scheme 76

have the same absolute configurations at the carbon atoms connected to the R^1 substituents. Several control experiments were conducted to clarify the reaction mechanism. When the zirconium-catalyzed reaction of hydrazone with vinyl ether was carried out after 3 h, the desired cycloaddition adduct was obtained with 54/46 *dr* along with 91% *ee* for the major isomer and 98% *ee* for the minor isomer, respectively. The selectivities are almost the same as those of the reaction for 18 h, suggesting that epimerization of the product (having an *N*,*O*-acetal moiety) did not occur during the reaction course. Further control experiments were cunducted by changing several reaction conditions, and the *ee*'s of the major and minor diastereoisomers are still clearly different. If the reaction proceeded via the stepwise pathway, the enantioselectivity of the major and minor diastereomers might be the same, and therefore, the above results suggest that the present reaction would proceed via the concerted pathway. In addition, the reaction of hydrazone with 2-methoxypropene as a representative of a 1-alkyl-substituted vinyl ether was also performed. It revealed that the reaction proceeded sluggishly under the standard reaction conditions. This result also suggests that the reaction would proceed via the concerted pathway, because an alkyl substituent at the 1-position of a vinyl ether would increase the nucleophilic addition of the vinyl ether to a hydrazone in the stepwise pathway but decrease the reactivity in the concerted pathway due to steric hindrance.

Leighton and coworkers have described a chiral silicon Lewis acid **155** for the highly diastereo- and enantioselective 1,3-dipolar cycloaddition of benzoylhydrazone and enolether (Scheme 77).[82c] The reactions are highly practical, as demonstrated by a larger

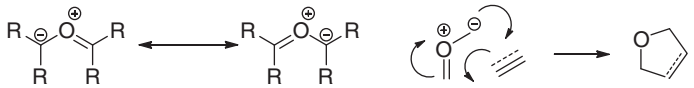


Scheme 77

scale reaction in which the product was obtained after recrystallization in 93% yield and 99% *ee*. Despite one equivalent of silane is required, the chiral pseudoephedrine **156** is easily recoverable in 99% yield. Control experiments indicated that the reaction undergoes a stepwise mechanism. By using this methord, they have also succeeded in the highly enantioselective synthesis of neuroprotective agent MS-153 and the total synthesis of optically active natural product Manzacidin C.[82d,e]

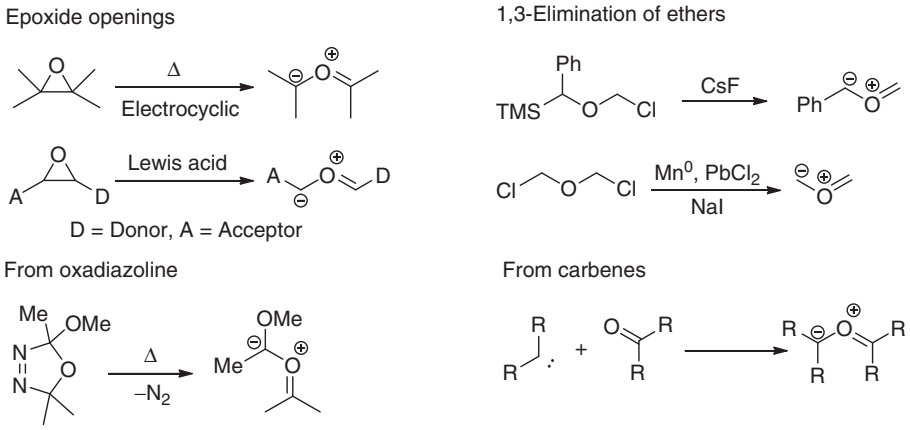
4.22.5 Carbonyl Ylides

Carbonyl ylides are very reactive candidates in the 1,3-dipolar cycloaddition with alkenes or alkynes (Scheme 78).



Scheme 78

Since carbonyl ylides are nonisolable, several protocols have been developed to generate them *in situ* (Scheme 79).[86] In asymmetric 1,3-dipolar cycloaddition reactions, the most important method to generate carbonyl ylides is the reaction of carbonyl group with carbenes, which are formed via decomposition of the diazo compound.[87] While using donor–acceptor oxiranes for *in situ*-carbonyl ylide generation, Zhang and coworkers recently have achieved substantial enantioselectivity in the [3+2] cycloaddition with indoles in the presence of Ni(II)/BOX catalysts.[86k]



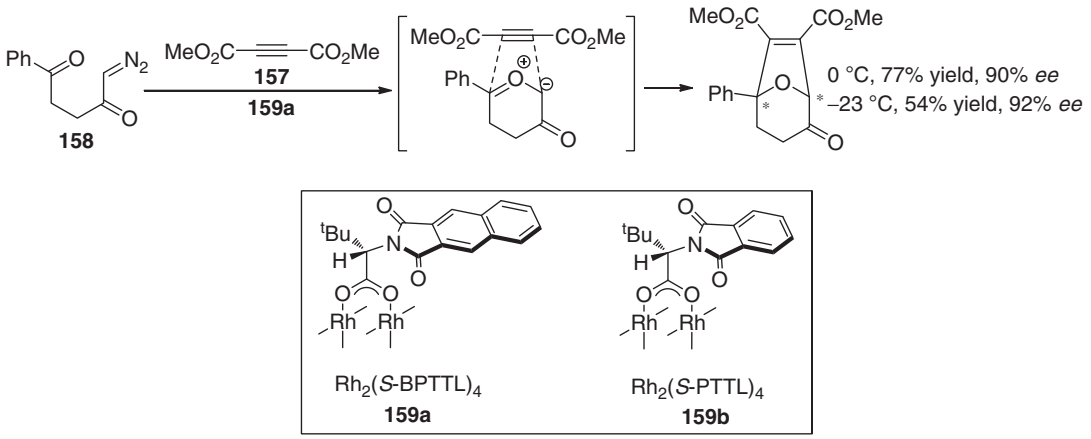
Scheme 79

In 1999, Hashimoto and coworkers have developed an enantioselective intermolecular 1,3-dipolar cycloaddition with dimethyl acetylene dicarboxylate **157** in tandem carbonyl ylide formation by α-diazo ketones **158** catalyzed by chiral dirhodium(II) carboxylate **159a** (Scheme 80).[87a]

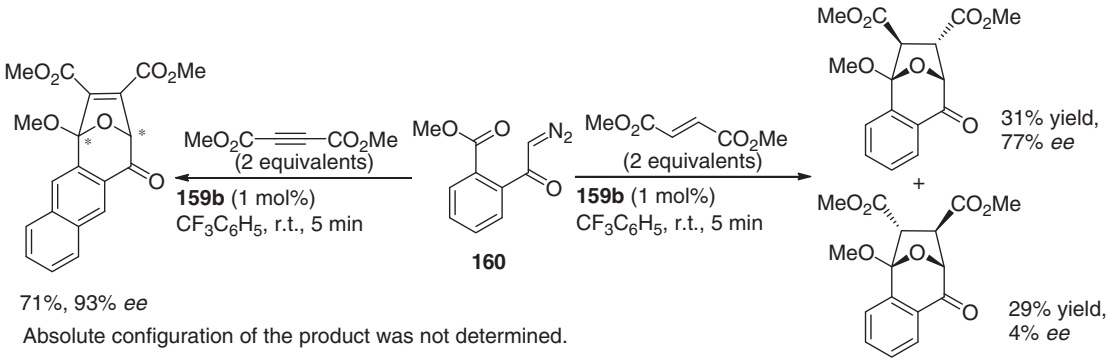
In 2000, they have applied this method to the asymmetric intermolecular 1,3-dipolar cycloaddition of dimethyl fumarate. The *in situ*-generated carbonyl ylide formed by decomposition of diazo compound **160** and an ester group was mediated by Rh_2(*S*-PTTL)$_4$ **159b** (Scheme 81).[87b]

In 2002, Suga and coworkers succeeded in carrying out highly enantioselective 1,3-dipolar cycloaddition reactions of 2-benzopyrylium-4-olate **161** and 3-acryloyl-2-oxazolidinone catalyzed by chiral Yb(III)–PyBOX-Ph **162** complexes (Scheme 82).[87c–e] The reaction was found to be effective in providing an *exo*-adduct **163** with extremely high enantioselectivity (98% *ee*).

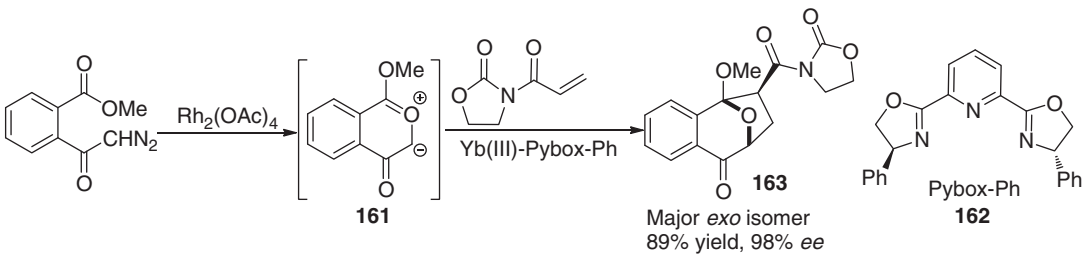
In 2007, they have found the first successful example of the 1,3-dipolar cycloaddition between inverse-electron-demand alkenes and carbonyl ylides (Scheme 83).[87f,g] In this dipole-LUMO/dipolarophile-HOMO controlled reaction, the carbonyl ylides



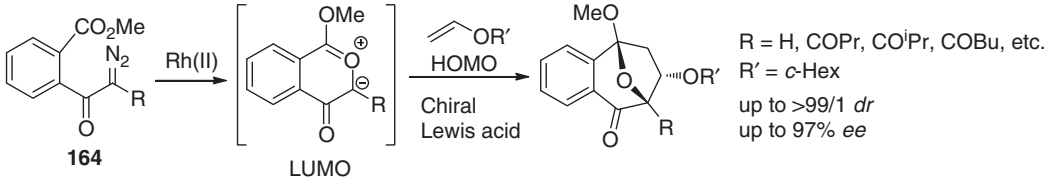
Scheme 80



Scheme 81



Scheme 82

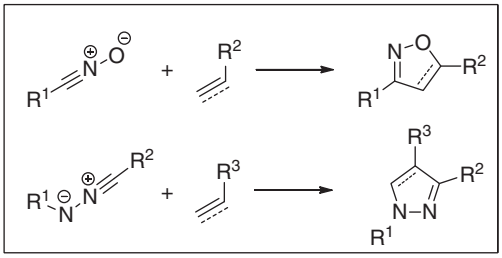


Scheme 83

were generated from *o*-methoxycarbonyl-*α*-diazoacetophenone **164** and their acyl derivatives as precursors, which were reacted with vinyl ether derivatives, giving high enantioselectivity (77–97% *ee*) via chiral 2,6-(oxazolinyl)pyridine–Eu(III) or BINIM–Ni (II) complexes as chiral Lewis acid catalysts.

4.22.6 Nitrile Oxides and Nitrile Imines

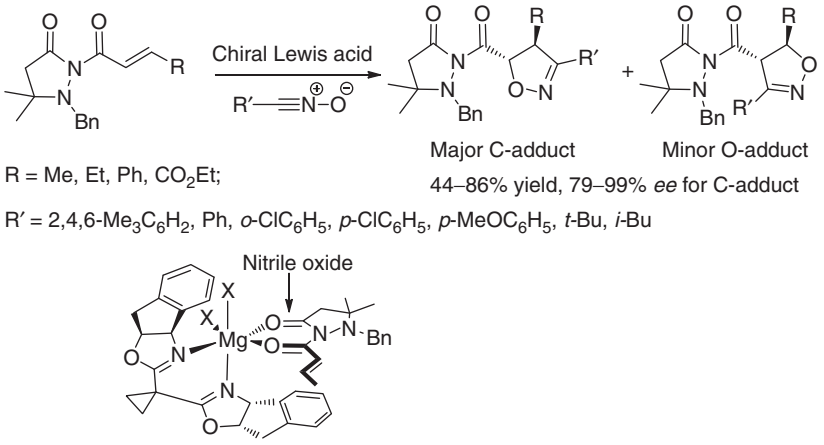
Nitrile oxide and nitrile imine are useful synthons in organic synthesis. They could be regarded as 1,3-dipoles, reacting with various alkenes and alkynes in 1,3-dipolar cycloadditions to build up the isoxazolines or pyrazoles (Scheme 84). Recently, the catalytic asymmetric cycloaddition of nitrile oxides or nitrile imines with alkenes has been studied and several successful methods have been developed.



Scheme 84

4.22.6.1 Catalytic Asymmetric 1,3-Dipolar Cycloadditions of Nitrile Oxides with Alkenes and Alkynes

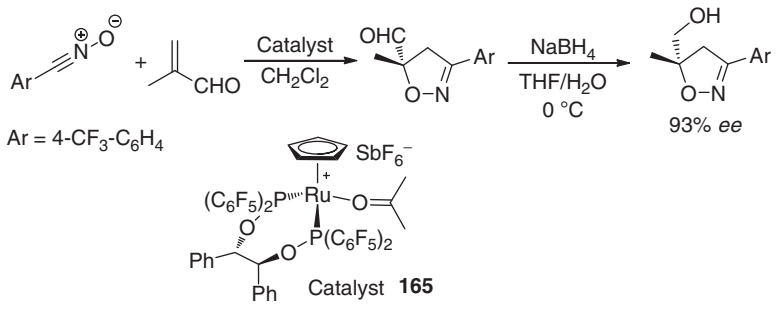
In 2004, Sibi and coworkers have described examples of highly regio- and enantioselective nitrile oxide cycloadditions to electron-deficient alkenes using substoichiometric amounts of a chiral Lewis acid (Scheme 85).[11a,88] Amberlyst 21 has been used as base to generate the unstable nitrile oxides from hydroximinoyl chlorides. This novel method could avoid potential problems involving coordination of the Lewis acid by amine bases. Pyrazolidinones proved to be effective achiral templates in the cycloadditions providing C-adducts typically in >30:1 selectivity and 80–99% *ee*.



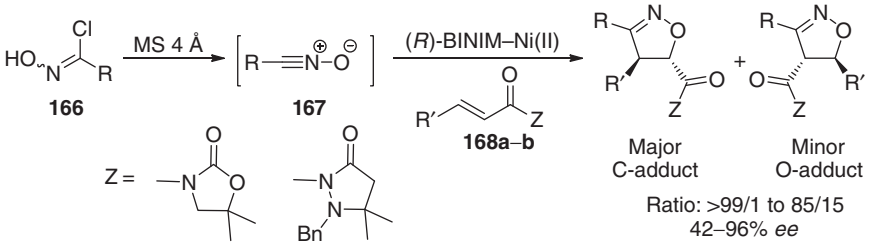
Scheme 85

In 2007, a transition metal Lewis acid **165** catalyzed the 1,3-dipolar cycloaddition reaction between aryl nitrile oxides and branched α,β-unsaturated aldehydes have been developed by Kündig and coworkers, to give chiral 2-isoxazolines with yield of 43–98% and enantioselectivity of 60–93% *ee* (Scheme 86).[89]

Recently, Suga and coworkers have disclosed a novel synthetic protocol featuring BINIM–Ni(II) complexes as chiral Lewis acid catalysts for the asymmetric cycloadditions of nitrile oxide (Scheme 87).[90] The nitrile oxides were generated from the corresponding hydroximoyl chloride **166** in the presence of MS 4 Å. The best result, in terms of enantioselectivity (96% *ee*), was achieved for the reaction of isolable 2,4,6-trimethylbenzonitrile oxide **167** and 3-crotonoyl-5,5-dimethyl-2-oxazolidinone **168a** as the dipolarophile. For the catalyzed cycloadditions of benzonitrile oxides with aliphatic nitrile oxides, the enantio- and regioselectivities were higher for pyrazolidinone **168b** as the dipolarophile than those using oxazolidinone. These results have contributed toward the development of chiral Lewis acid-catalyzed asymmetric cycloaddition reactions of unstable 1,3-dipoles.



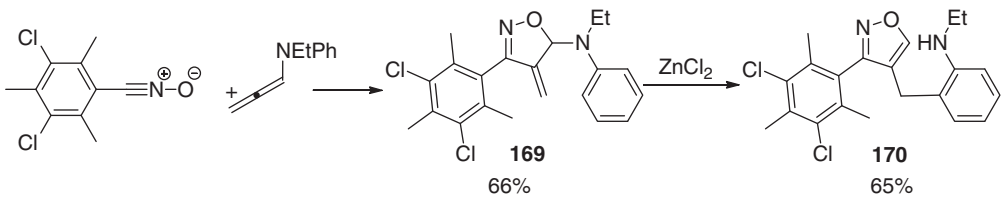
Scheme 86



Scheme 87

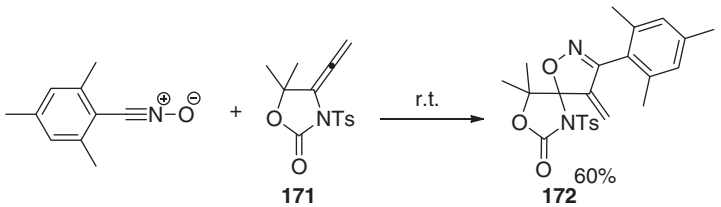
4.22.6.2 1,3-Dipolar Cycloadditions of Nitrile Oxide with Allenes

Nitrile oxides could undergo 1,3-dipolar cycloaddition with allenes. As shown below, a variety of products **169** were formed depending on the substituents of both nitrile oxide and allene (Scheme 88).[91] As reported by Broggini and Zecchi, the cycloadduct was slowly converted to the isomeric isoxazole **170** in the presence of $ZnCl_2$ via a Claisen-type rearrangement.[91a]



Scheme 88

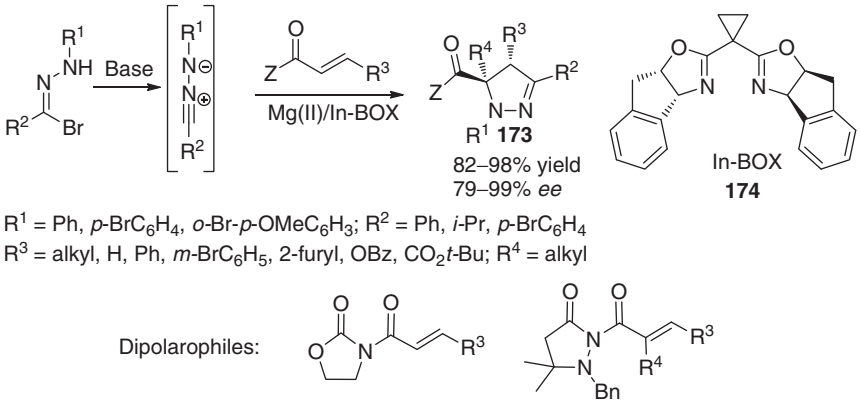
In 2003, Tamaru and coworkers described that 4-vinylideneoxazolidin-2-one **171** could react with nitrile oxide at the internal C═C bond smoothly at room temperature, furnishing the diazadioxaspiro compound **172** in moderate yield (Scheme 89).[91b]



Scheme 89

4.22.6.3 Catalytic Asymmetric 1,3-Dipolar Cycloadditions of Nitrile Imines with Alkenes and Alkynes

In 2005, Sibi and coworkers have developed a promising protocol to access optically active dihydropyrazoles **173** from 1,3-dipolar cycloaddition of electron-deficient olefins and *in situ*-generated nitrile imines (Scheme 90).[92] The reaction proceeds smoothly with high regio- and enantioselectivity using chiral Mg(II)/In–BOX **174** complex as catalyst.



Scheme 90

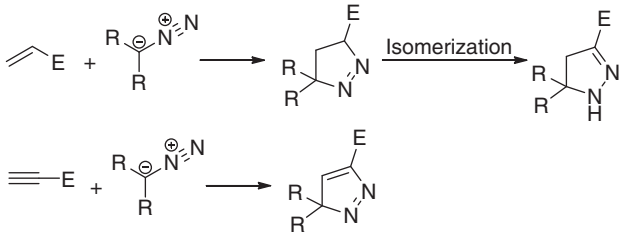
In the use of this strategy, they have succeeded in preparing dihydropyrazoles bearing a chiral quaternary center at the 5-position, employing α,β-disubstituted-α,β-unsaturated carbonyl substrates as dipolarophiles.[93]

4.22.7 Diazoalkanes

Diazoalkane has two linked nitrogen atoms (azo) as a terminal functional group. The general formula is $R_2C{=}N_2$. The electronic structure of diazoalkane involves a positive charge on the central nitrogen and negative charge distributed between the terminal nitrogen and the carbon (Figure 9).

Figure 9 Electronic structure of diazoalkanes.

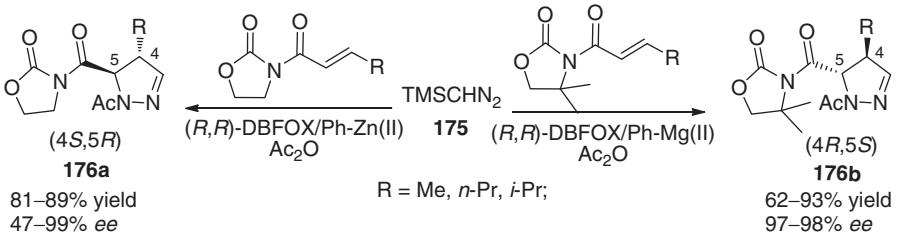
Cycloaddition of diazoalkanes with olefins results in Δ^1-pyrazolines, which could isomerize to Δ^2-pyrazolines (Scheme 91). With acetylenic dipolarophiles, the reactions lead to pyrazoles. For simple diazoalkanes, the cycloaddition process could be promoted by electron-withdrawing substituents on the dipolarophiles.



Scheme 91

4.22.7.1 Catalytic Asymmetric 1,3-Dipolar Cycloadditions of Diazoalkanes with Alkenes

In 2000, Kanemasa and coworkers have developed an effective enantioselective 1,3-dipolar cycloadditions of diazoalkane with electron-deficient alkenes catalyzed by a Lewis acid (Scheme 92).[94] In this reaction, the enantioselectivity of the cycloadducts is

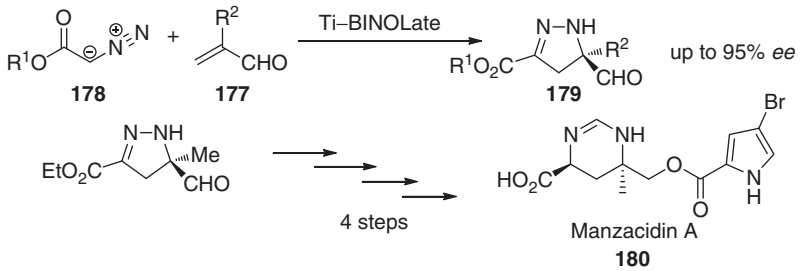


Scheme 92

controlled by the cooperation of the chiral ligand and achiral chelating auxiliary. The almost complete switch of enantioselectivity has been achieved simply by adding substituents to the same achiral chelating auxiliary.

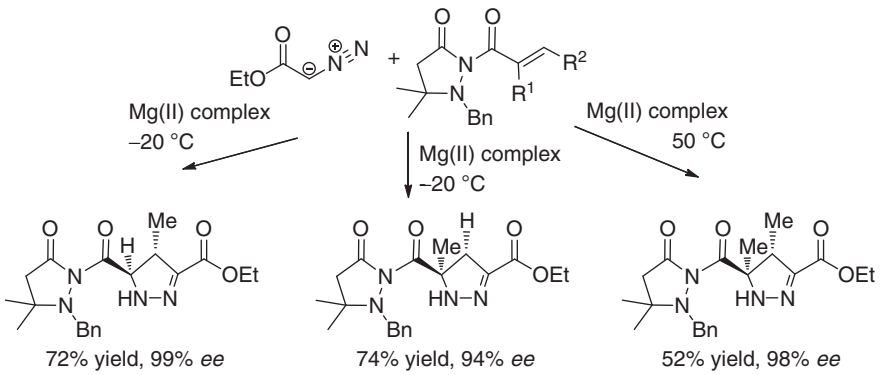
In the presence of the (*R*,*R*)-DBFOX/Ph-Zn(II) complexes, the reaction of 3-crotonoyl-2-oxazolidinone with trimethylsilyldiazomethane **175** furnishes (4*S*,5*R*)-1-acetyl-5-(2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline **176a** in 99% *ee*. However, the reaction of 3-crotonoyl-4,4-dimethyl-2-oxazolidinone with trimethylsilyldiazomethane **175** catalyzed by the (*R*,*R*)-DBFOX/Ph-Mg(II) gives (4*R*,5*S*)-1-acetyl-5-(4,4-dimethyl-2-oxo-3-oxazolidinylcarbonyl)-2-pyrazoline **176b** in 97% *ee*.

Since this successful example has been reported, there were few achievements contributed to this field until 2006. Maruoka and coworkers have developed a titanium BINOLate-catalyzed asymmetric 1,3-dipolar cycloaddition reaction between α-substituted acroleins **177** and alkyl diazoacetates **178**, affording chiral 2-pyrazolines **179** with a quaternary stereogenic center in high to excellent enantioselectivities (up to 95% *ee*).[95] Applying this methodology, optical active manzacidin A[96] **180** was successfully synthesized in five steps, starting from commercially available methacrolein and ethyl diazoacetate (Scheme 93).



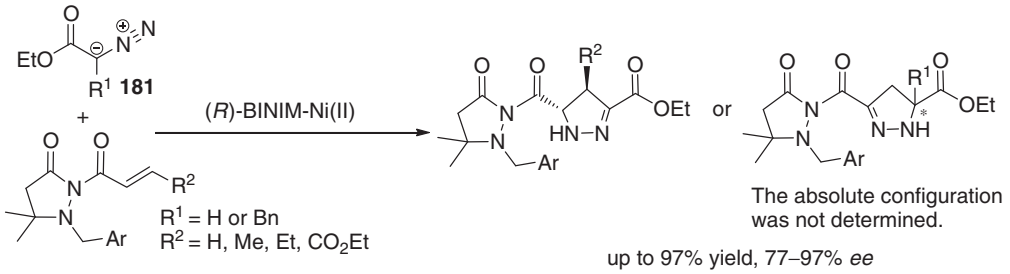
Scheme 93

In 2007, Sibi and coworkers have demonstrated a general strategy for highly enantioselective 1,3-dipolar cycloaddition of diazoesters to multisubstituted olefins (Scheme 94).[97] The methodology allows facile access to enantioenriched pyrazolines derived from α-substituted, β-substituted, and α,β-disubstituted, unsaturated pyrazolidinone imides via Mg(II)/In–BOX complex as catalyst. In this cycloaddition, when less reactive α,β-disubstituted dipolarophiles were utilized, elevated reaction temperatures were required, but still provide the corresponding pyrazolines with excellent enantioselectivities (up to 99% *ee*).



Scheme 94

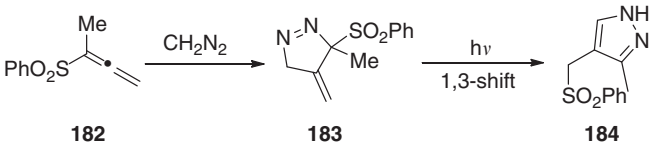
Recently, Suga and coworkers have described the chiral (*R*)-BINIM–Ni(II)-catalyzed asymmetric 1,3-dipolar cycloaddition reactions between ethyl diazoacetate **181** and 2-(2-alkenoyl)-3-pyrazolidinone derivatives in the selective formation of 2-pyrazolines with high enantioselectivity (up to 97% *ee*) (Scheme 95).[98] The asymmetric induction was found to be affected by both the counteranion of the Ni(II) complex and the 4-substituent of the quinoline ring on the BINIM ligand. In the presence of the BINIM–Ni(II) catalyst, relatively good enantioselectivity (up to 77% *ee*) was also observed in the reactions of an *α*-substituted diazo ester with 2-acryloyl-3-pyrazolidinone derivatives.



Scheme 95

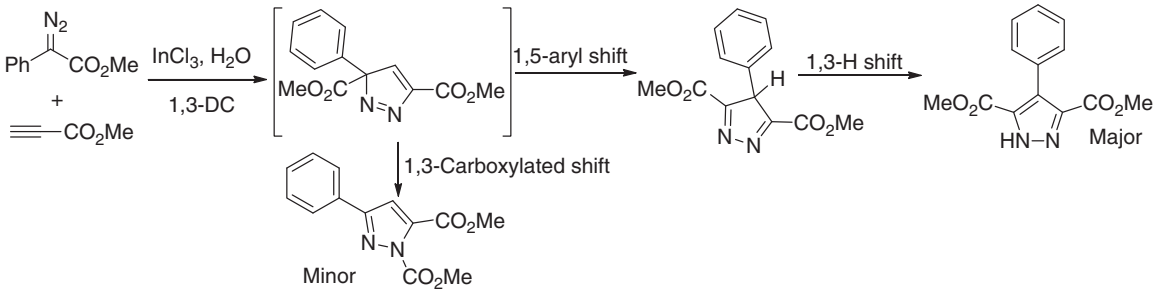
4.22.7.2 1,3-Dipolar Cycloadditions of Diazoalkanes with Allenes and Alkynes

The addition of allene to diazomethane gives 4-methylene-1-pyrazoline. A reaction of 3-(phenylsulfonyl)-1,2-butadiene **182** and diazomethane has been described by Padwa and coworkers, affording the corresponding pyrazoline**183** in 80% yield (Scheme 96).[99] On irradiation with a 300-nm sunlamp, disubstituted pyrazole **184** was provided undergoing a 1,3-sulfonyl shift.



Scheme 96

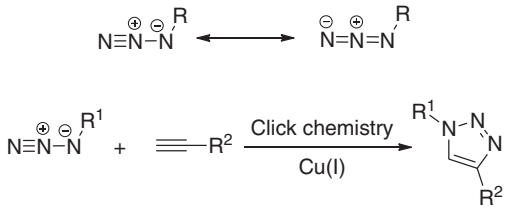
In 2004, Li and coworkers have disclosed the first intermolecular 1,3-dipolar cycloaddition of diazocarbonyl compounds with alkynes (Scheme 97).[100] $InCl_3$ has been employed as catalyst and the cycloaddition was conducted in water. The process is practical and is applicable to various *α*-diazocarbonyl compounds and alkynes with a carbonyl group at the neighboring position to generate a wide range of pyrazoles. The reaction was found to proceed by a domino 1,3-dipolar cycloaddition–hydrogen (alkyl or aryl) migration.



Scheme 97

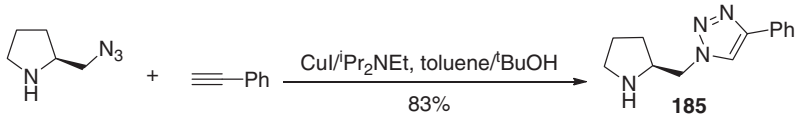
4.22.8 Azides

Among the 1,3-dipolar cycloaddition reactions, click chemistry is an efficient method for the construction of triazole derivatives by the cycloaddition of azides and acetylenes. This copper(I)-catalyzed cycloaddition reaction achieved high regioselectivity together with high yield under ambient conditions (Scheme 98).[101]



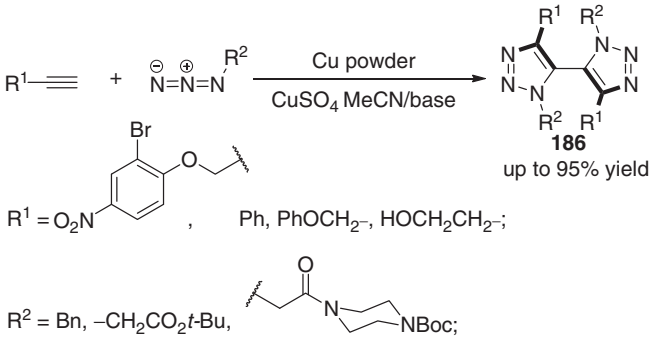
Scheme 98

Since Sharpless reported the click chemistry of azides, this area has become of great interest, and much effort has been devoted, including a range of 1,3-dipolar cycloaddition reactions of azides and alkynes to build up useful triazole moieties in organic synthesis.[102] In 2006, Cheng and coworkers have employed this methodology to construct a library of the pyrrolidine-type asymmetric organocatalysts **185** (Scheme 99).[102a] The triazole–pyrrolidine organocatalysts have been successfully applied to the asymmetric Michael addition of ketones to nitroolefins.



Scheme 99

Burgess and coworkers have developed the copper-mediated click reaction of alkynes and azides via a carbonate base as an additive, leading to an oxidative coupling to form predominately 5,5′-bistriazoles **186** (Scheme 100).[102b]

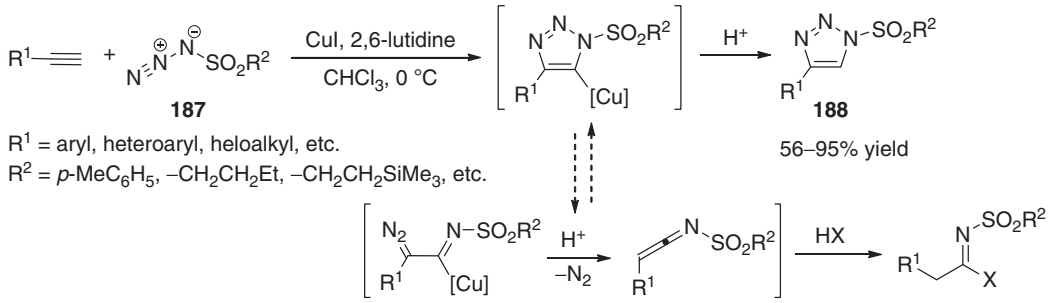


Scheme 100

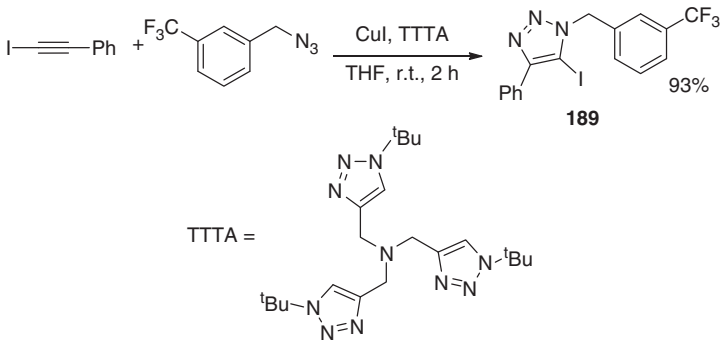
A Cu-catalyzed 1,3-dipolar cycloaddition reaction of alkynes with sulfonyl azides **187** has been demonstrated by Fokin and coworkers (Scheme 101).[102f] The reaction was carried out at 0 °C in chloroform in the presence of 2,6-lutidine and CuI as the catalyst. Under the reaction conditions, the ketenimine pathway has been effectively prevented and selectively gives a convenient access to *N*-sulfonyltriazoles **188** in good to excellent yield.

Recently, Moses and coworkers have developed an efficient one-pot protocol to trisubstituted triazoles **189** in excellent yield with high regioselectivity (Scheme 102).[102i]

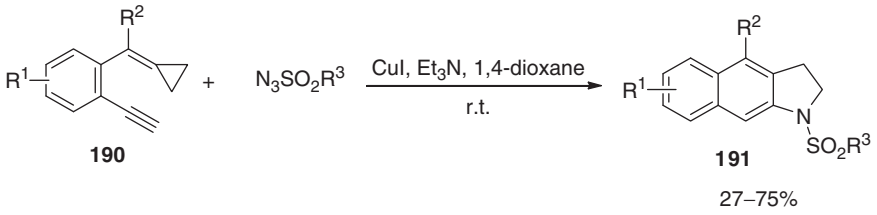
Wu and coworkers have explored a cascade reaction of 2-ethynylaryl methylene cyclopropane **190** with sulfonyl azide under mild conditions, which involves a Cu-catalyzed azide–alkyne cycloaddition in the first step (Scheme 103).[102k] This method provides a novel and efficient route for the synthesis of substituted fused indulines **191**.



Scheme 101



Scheme 102



Scheme 103

4.22.9 Conclusion

In the past two decades, a plenty of 1,3-dipoles containing various combinations of carbon and heteroatoms have attracted much attention and their reactions with a variety of dipolarophiles, including versatile alkenes, alkynes, and allenes, have been developed vigorously, especially in the asymmetric catalysis field. Several successful catalyst systems have been developed in terms of chiral Lewis acids as well as chiral organocatalysts. For the 1,3-dipolar cycloaddition of nitrones with electron-deficient alkenes, such as enamides, enals, and enones as well as electron-rich alkenes, such as ketene acetals and alkyl vinyl ethers, abundant research has been carried out and very often reached excellent yield and stereoselectivities. The enantioselective catalytic Kinugasa reaction of alkynes with nitrones has attracted intensive studies. The reaction between nitrones and allenes takes place regioselectively. The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylide with considerable α,β-unsaturated carboxylic derivatives, nitroalkenes, alkenylsulfones, and enones has been developed using various chiral catalyst systems such as Cu(I), Cu (II), Ag(I), Ni(II), and Ca(II) complexes of different chiral ligands (e.g., BOX, BINAP, Quinap, and ferrocenyl phosphines). Organocatalysts have also shown its promising ability in the enantiocontrol of catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with α,β-unsaturated aldehydes and allenes. *N,N′*-cyclic azomethine imines has been employed widely in the asymmetric 1,3-dipolar cycloadditions; *C,N*-cyclic azomethine imines have been developed as another type of azomethine imines, and their property and synthetic utility in the asymmetric 1,3-dipolar cycloadditions have been documented. Hydrazones have been used as acyclic azomethine imine analogs in the asymmetric 1,3-dipolar cycloadditions with electron-rich olefins.

Organocatalyst such as chiral dicarboxylic acid has also showed good performance in the field of azomethine imines involved 1,3-dipolar cycloadditions. The *in situ*-generated carbonyl ylides with dimethyl acetylene dicarboxylate, dimethyl fumarate, 3-acryloyl-2-oxazolidinone, and vinyl ether derivatives have been documented. New strategies for cycloadditions of nitrile oxides with electron-deficient alkenes and allenes, as well as nitrile imines with enamides have been disclosed. Reactions of diazoalkanes with diverse enamides, branched aldehydes, allenes, and methyl propiolate have been documented catalyzing a variety of different Lewis acids. In addition, the emergence of click chemistry by the cycloaddition of azides and acetylenes provides an efficient method for the construction of triazole derivatives. However, limitations are still found, especially for the cycloadditions of carbonyl ylides, nitrile oxides, nitrile imines, and diazoalkane. Most reactions are promoted by Lewis acid catalysis; few organocatalysts have been applied in this area; and only a few examples with limited substrate scopes have been shown. As some 1,3-dipoles are unstable and nonisolable, design of easy operated 1,3-dipoles and new strategies to the 1,3-dipolar cycloadditons with different dipolarophiles still requires further development. The application of these strategies, which offered facile access to complex structures, will attract increasing interest in the future.

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4.23 Stetter Reaction

M Gravel and JM Holmes, University of Saskatchewan, Saskatoon, SK, Canada

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Glossary

Acyl anion equivalent A species that formally reacts as an acyl anion.

Breslow intermediate A nucleophilic enolamine intermediate formed during Stetter and benzoin reactions.

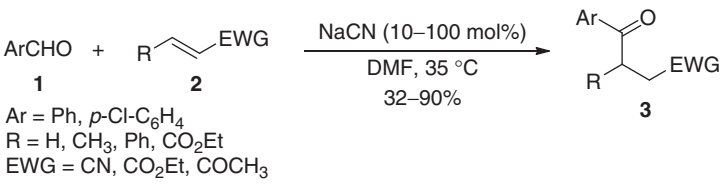
Hydroacylation The addition of an aldehyde onto an unactivated alkene.

NHC *N*-heterocyclic carbene.

Stetter reaction The addition of an aldehyde onto an α,β-unsaturated compound.

4.23.1 Introduction

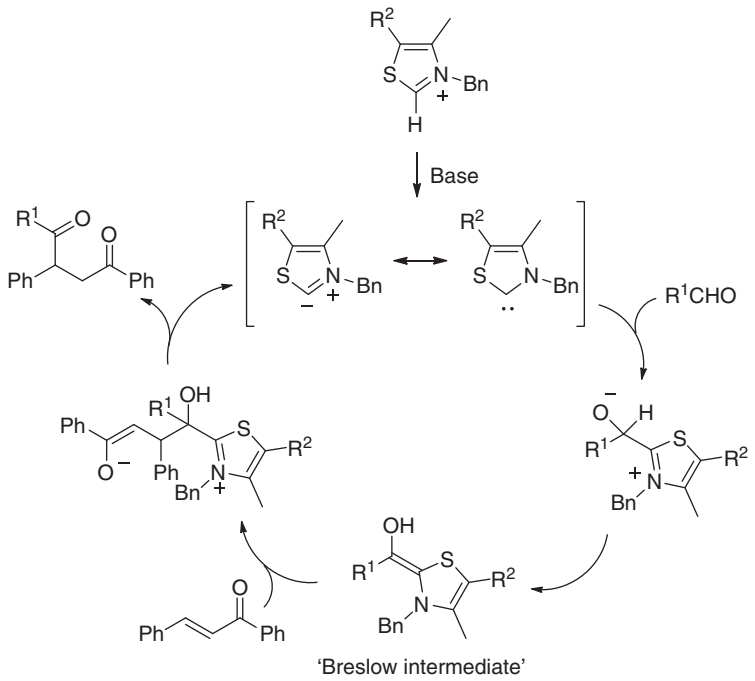
The formation of a new carbon–carbon bond between an aldehyde-derived acyl anion equivalent and a Michael acceptor was first reported by Stetter and Schreckenberg in 1973 (equation 1).[1]



(1)

The reaction, now commonly known as the Stetter reaction,[2,3] is closely related conceptually and mechanistically to the benzoin (acyloin) reaction. In the original discovery, the cyanide anion was used to catalyze the coupling of unsaturated nitriles, esters, or ketones with aromatic aldehydes. In contrast, enolizable aliphatic aldehydes were found to undergo aldol condensation because of the high basicity of the cyanide ion. A solution to this problem was quickly devised through the use of thiazolium salts and triethylamine.[4] Under basic conditions, a variety of azolium salts undergo deprotonation to generate a zwitterionic species, often depicted as their *N*-heterocyclic carbene (NHC) mesomeric form. The generally accepted mechanism of the NHC-catalyzed Stetter reaction involves the formation of an enolamine or 'Breslow intermediate,' as had previously been suggested for the benzoin reaction (Scheme 1).[5] The Breslow intermediate attacks the Michael acceptor in a conjugate addition, ultimately

 doi:10.1016/B978-0-08-097742-3.00429-8



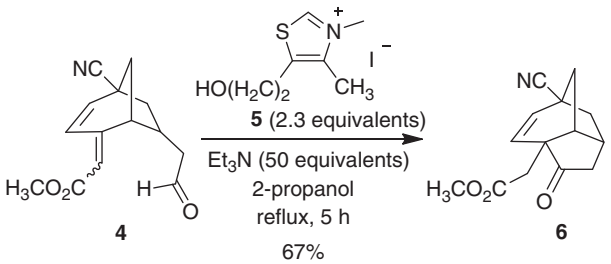
Scheme 1 Mechanism of the thiazolium-catalyzed Stetter reaction.

delivering the Stetter product. As was noted earlier, attack of the Breslow intermediate onto a second molecule of aldehyde leads instead to the benzoin product, an α-hydroxy ketone. This reversible pathway is usually kinetically favored and the benzoin product can therefore be obtained under kinetic control. As the Stetter product is generally thermodynamically favored, α-hydroxy ketones can replace the aldehyde as substrate in a Stetter-like reaction.[1]

The range of catalysts used for this reaction has since been extended to include other azolium salts. Owing to their ease of synthesis and the availability of a large number of chiral precursors, 1,2,4-triazolium salts have established themselves as the preferred catalyst framework for Stetter reactions. Interestingly, trialkylphosphines were shown to catalyze the reaction between aromatic aldehydes and unsubstituted acrylamides in the absence of additional base.[6] The substrate scope in both the aldehyde and Michael acceptor has also increased to include a variety of functional groups. In 2008, Hawkes and Yates reported a DFT study which essentially supports the mechanism shown in Scheme 1.[7]

4.23.2 Intramolecular Stetter Reactions

In their 1979 total synthesis of (±)-hirsutic acid, Trost et al. reported the first intramolecular Stetter reaction (equation 2).[8] The difficult transformation of aldehyde **4** to the key intermediate tricyclic ketone **6** required an excess (2.3 equivalents) of the readily available thiazolium salt **5** to afford the product in good yield. Notably, this work also represented the first formation of a quaternary center via the Stetter reaction.



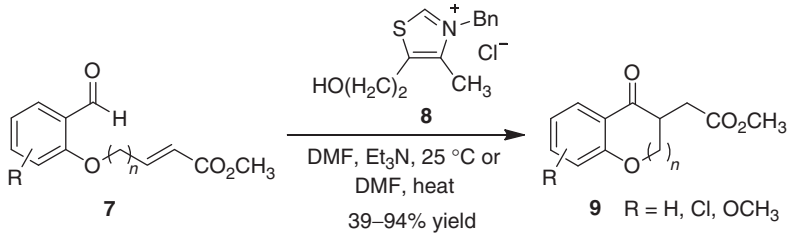
(2)

Following a dormancy period, the intramolecular Stetter reaction has been the object of increased attention from various groups.

4.23.2.1 Synthesis of Benzannulated Systems

The intramolecular Stetter reaction received little attention until the first catalytic intramolecular Stetter reaction was reported by Ciganek in 1995.[9] By tethering Stetter acceptors onto the salicylaldehyde framework, Ciganek was able to access 4-chromanones

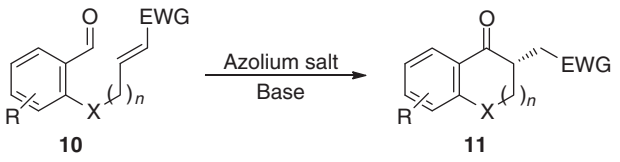
(**9**, $n=1$) in 86–94% yields (equation 3). Base-sensitive benzannulated furanones (**9**, $n=0$) were also obtained in modest yield (39–52%) when dimethylformamide and heat were employed to deprotonate the precatalyst, in lieu of base (equation 3, $n=0$). Notably, cyanide did not promote the intramolecular Stetter reaction, as it was consumed in a competing Michael-aldol reaction. Although Ciganek's report was limited to the formation of racemic products, his *ortho*-substituted benzaldehyde scaffold provided the inspiration for a series of studies on the enantioselective intramolecular Stetter reaction.



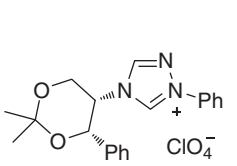
7 **8** **9** R = H, Cl, OCH_3 (3)

Closely following Ciganek's report, Enders et al. reported the first enantioselective, intramolecular Stetter reaction (**Table 1**).[10] By employing chiral triazolium salt **12** as precatalyst, Enders was able to access 4-chromanones (**11**, X=O, $n=1$) in generally modest enantioselectivity (46–74% *ee*) and yields (22–73%). In 2002, Rovis and coworkers demonstrated that high enantioselectivities could be achieved using rigid aminoindanol-derived triazolium salts.[11,12] In Rovis' seminal report, a variety of highly enantioenriched benzannulated products were obtained when chiral triazolium salt **13** was employed. Although 4-chromanones were generally obtained in excellent yields, nitrogen and sulfur-tethered Michael acceptors afforded products in slightly lower yields and an alkyl-tethered acceptor required a less sterically bulky triazolium salt (**29**) to afford a satisfactory yield. The use of a vinylogous carbonate substrate (X=O, $n=0$) afforded a racemic benzofuranone because of base-catalyzed racemization of the product, whereas the use of a longer tether (X=O, $n=2$) led only to starting material recovery.[13] Subsequent studies revealed that in addition to esters, ketones, nitriles,[14] thioesters, Weinreb amides,[13] phosphine oxides, phosphonates,[15] and acyl pyrroles[16] could be used as the electron-withdrawing group in the acceptor moiety for 4-chromanone synthesis (X=O, $n=1$). However, unsaturated *N*,*N*-dialkyl amides proved unreactive whereas the use of enals and nitroolefins favored other reaction pathways. Interestingly, it was also observed that unsaturated esters with *Z* geometry were unreactive under the optimized reaction conditions. From a practical perspective, these reactions were found to be quite sensitive to adventitious moisture and oxygen.[13]

Table 1 Synthesis of chroman-4-ones and benzofuran-3-ones via intramolecular Stetter reactions

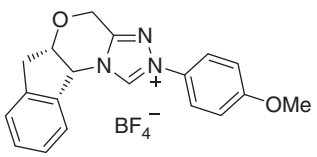


10 **11**



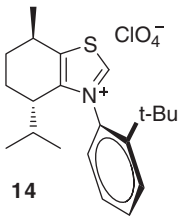
12

Enders 1996 — 22–73% yield, 41–74% *ee*



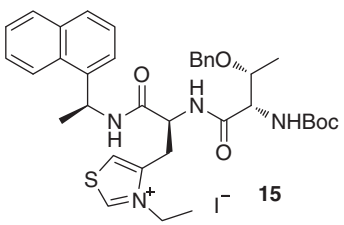
13

Rovis 2002 — 35–95% yield, 84–96% *ee*



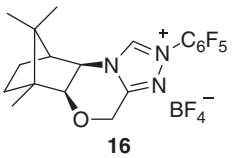
14

Bach 2004 — 75% yield, 50% *ee*



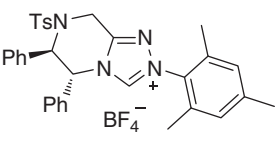
15

Miller 2004 — 39–88% yield, 0–75% *ee*



16

You 2011 — up to 96% yield, up to 96% *ee*



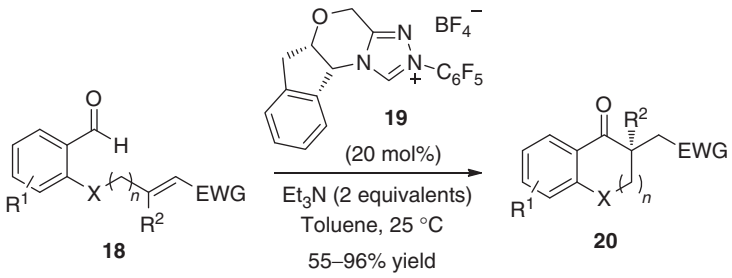
17

You 2011 — up to 98% yield, up to 97% *ee*

Continuous bubbling of argon through the reaction medium was shown to efficiently exclude oxygen, whereas addition of water scavengers such as molecular sieves, sodium sulfate, or magnesium sulfate improved yields when using ACS-grade solvents, albeit with slightly reduced enantioselectivity.

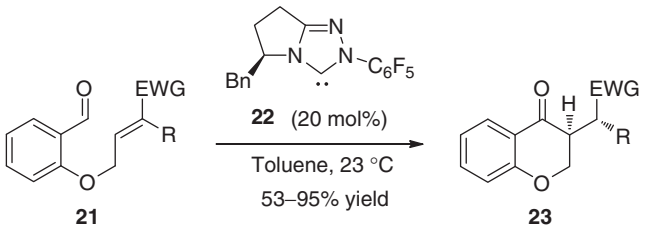
In 2004, Bach and coworkers reported the use of axially chiral thiazolium precatalyst **14** in the modestly enantioselective synthesis of a 4-chromanone (X=O, $n=1$).[17] The poor stereoselectivity of Bach's methodology is attributed to the base-promoted isomerization of precatalyst **14** to its atropisomer. Miller and coworkers screened a number of peptides bearing a thiazolium substituent for their ability to promote enantioselective intramolecular Stetter reactions.[18] In the event, thiazolium salt **15** afforded 4-chromanones (X=O, $n=1$) in low to good enantiomeric excess and in modest to good yields. Low enantiomeric excess values were attributed, in part, to the reaction conditions promoting racemization of the product. In 2011, You and coworkers reported highly enantioselective syntheses of 4-chromanones employing camphor-derived triazolium salt **16** as precatalyst for the Stetter reaction (X=O, $n=1$).[19] Under the standard reaction conditions, a sulfur-tethered acceptor (X=S, $n=1$) also afforded the product with good enantiomeric excess (88% *ee*) albeit in low yield (26%), whereas a nitrogen-tethered acceptor (X=NMs, $n=1$) afforded the cyclized product in modest enantiomeric excess (56% *ee*) and good yield (77%). Similar results were reported for reactions using (1*R*,2*R*)-diphenylethylenediamine-derived triazolium salt **17**, although a better yield (70%) was obtained for the sulfur-containing substrate (X=S, $n=1$).[20] The use of a shorter tether (X=O, $n=0$) successfully provided the desired benzofuranone, although the basic reaction conditions (base=Et_3N) led to complete racemization of the product.

In related work, Kerr and Rovis showed in 2004 that benzofuranones bearing a quaternary center can also be formed with high enantioselectivity (equation 4).[21] In contrast to results obtained with β-mono-substituted substrates, the use of an electron-poor *N*-aryl substituent on the triazolium salt led to higher conversions. Using catalyst **19**,[22] the cyclization products **20** ($n=0$) were obtained in very high yield (92–96%) and enantioselectivity (89–99% *ee*) with a variety of tethers (X=O, S, CH_2) and an ester as the electron-withdrawing group. It was later found that the use of KO*t*-Bu as base improved the yield and enantioselectivity for a range of thioether-tethered substrates.[23] Performing the ring closure on a longer tether (X=O, $n=1$) proved more challenging, and a moderate yield (55%) of the 4-chromanone was obtained when using a ketone as the electron-withdrawing group.



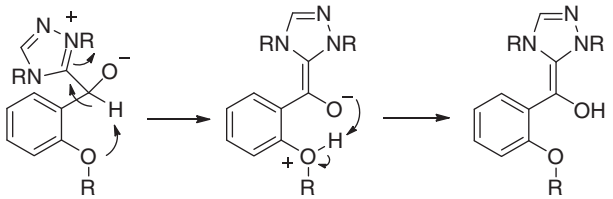
(4)

The synthesis of 4-chromanones via intramolecular Stetter reactions was extended to the formation of two contiguous stereogenic centers when utilizing α,α-disubstituted Michael acceptors **21** (equation 5).[24] Results using olefin isomers suggest an intramolecular protonation of the enolate formed during the conjugate addition. Owing to the ease of epimerization of the products **23**, it was found necessary to reduce the basicity of the reaction mixture by preforming the carbene catalyst **22** and removing the volatile hexamethyldisilazane before addition of the substrate. The use of an electron-poor *N*-aryl substituent on the triazolium salt also helped minimize epimerization. Under these conditions, a variety of unsaturated esters, lactones, and ketones could provide the cyclized products in high diastereo- and enantioselectivity (up to 35:1 *dr*, up to 95% *ee*).



(5)

Throughout these studies on the formation of benzannulated systems, O-tethered substrates derived from salicylaldehyde have generally led to higher yields and/or faster reactions than their methylene-tethered counterparts. In order to shed light on this issue and with the view of expanding the reaction scope, Rovis and coworkers performed mechanistic studies.[25] Through deuterium labeling and competition experiments, they determined that the first irreversible step is a proton transfer during formation of the Breslow intermediate. The authors suggest that the oxygen atom in the tether facilitates this step by acting as a proton shuttle (**Scheme 2**). This study thus also demonstrates that the turnover-limiting step and the enantioselectivity-determining step may be distinct in Stetter reactions. Domingo et al. performed a theoretical study at the B3LYP/6-31G** level using the simplified *N*,*N*′-dimethyltriazolylidene as catalyst.[26] Their findings support the notion that proton transfer en route to the Breslow intermediate is rate-determining, although a pathway involving oxygen participation was not discussed.



24 **25** **26**

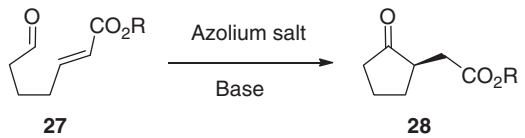
Scheme 2 Formation of Breslow intermediate in salicylaldehyde derivatives.

4.23.2.2 Synthesis of Alicyclic Systems

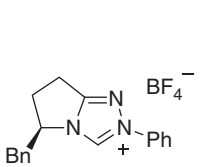
Generally, intramolecular Stetter reactions on aliphatic aldehydes have proven more difficult than the ones involving aromatic aldehydes, partly for entropic reasons. Nevertheless, a number of synthetically useful methodologies have been developed over the years.

In 2002, Rovis and coworkers provided a single example of a cyclopentanone-forming Stetter cyclization (Table 2).[11] Using phenylalanine-derived triazolium salt **29**, α-substituted cyclopentanone **28** (R=Et) was formed in high yield and enantiomeric excess. The low acidity of the resulting alicyclic ketone avoided racemization problems encountered when forming benzofuranone products. In 2006, Matsumoto and Tomioka reported the use of chiral C_2-symmetric imidazolinium **30** in the enantioselective synthesis of cyclopentanone **28** (R=*t*Bu).[27] The nature of the nitrogen substituents on the imidazolinium salt was found to have a profound impact on the yield and enantioselectivity of the reaction. This methodology represents a rare example of the use of imidazolinium or imidazolium salts as catalysts for the Stetter reaction.

Table 2 Enantioselective α-substituted cyclopentanone formation

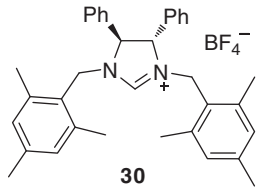


27 **28**



29

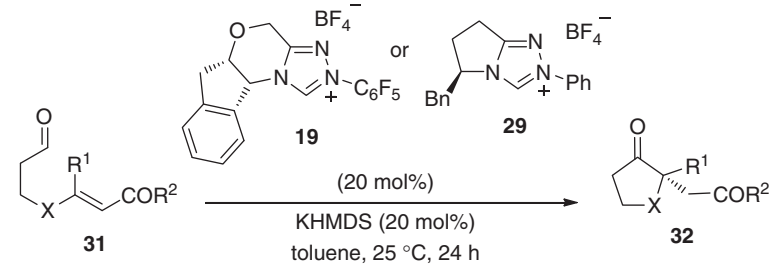
Rovis 2002: 81% yield, 95% *ee*



30

Matsumoto Tomioka, 2006: 59% yield, 80% *ee*

As was the case for benzannulated systems, cyclopentanones **32** bearing a new quaternary stereocenter could be efficiently synthesized using triazolium catalysts bearing an *N*-C_6F_5 substituent (equation 6).[21,23] Unlike cases in which a tertiary stereocenter is formed (cf. equation 6), the use of an ester as the single electron-withdrawing group on the acceptor **31** does not impart sufficient electrophilicity on the acceptor for the reaction to proceed. However, the use of unsaturated ketones or doubly activated alkenes lends itself well to this reaction. A variety of tethers are tolerated in this transformation (X=S, SO_2, NAc, CH_2), as well as α-unbranched alkyl substituents (R^1). Of note, the *E* geometry of the alkene is essential to obtain both high yields and enantiomeric excess.



19 **29**

31

X = SO_2, NAc, CH_2
R^1 = Me, Pr, *n*-Bu
R^2 = OMe, Alkyl, Ar

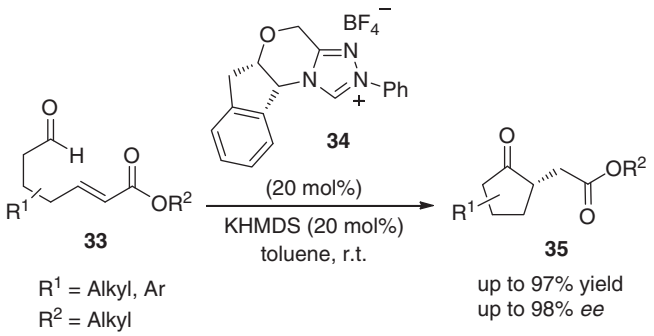
(20 mol%)
KHMDS (20 mol%)
toluene, 25 °C, 24 h

32

63–98% yield
80–99% *ee*

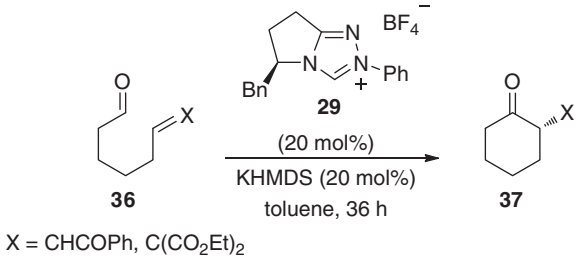
(6)

The effect of preexisting stereogenic centers on the acyclic substrates was investigated by Reynolds and Rovis (equation 7).[28] These studies determined that the formation of 2,3- or 2,4-disubstituted cyclopentanones occurs under catalyst control, whereas the formation of 2,5-disubstituted cyclopentanones is under substrate control and kinetically favors the *cis* product.



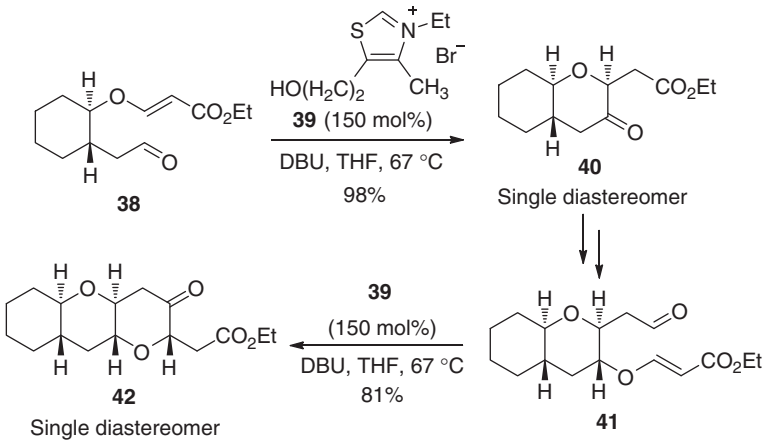
(7)

The formation of cyclohexanones **37** via intramolecular Stetter reactions has proven much more challenging than that of cyclopentanones. For instance, aliphatic substrates **36** bearing an ester (X=$CHCO_2Et$) or a methyl ketone (X=CHCOMe) were left unreacted under conditions that were used for the formation of the analogous cyclopentanone (equation 8).[14] Use of the more electrophilic phenyl ketone (X=CHCOPh) led to the desired product in modest enantioselectivity (42% *ee*, 60% yield).[13] However, the use of substrate **36** bearing a highly electrophilic alkylidene malonate acceptor (X=$C(CO_2Et)_2$) led to smooth formation of the cyclized product in good enantioselectivity (82% *ee*, 97% yield).



(8)

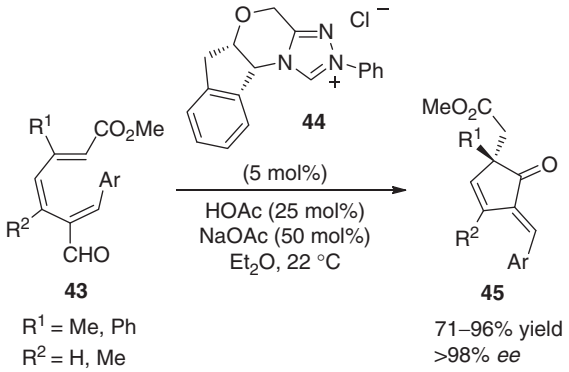
In 2009, McErlean and Willis disclosed an elegant application of the intramolecular Stetter reaction to access polycyclic ether frameworks in an iterative manner (**Scheme 3**).[29] In this approach, formation of the six-membered pyranone is entropically facilitated by the presence of a cyclic tether. Although direct formation of seven-membered oxepanones was not possible using a Stetter reaction, ring expansion of the corresponding pyranone was shown to be a viable route. Subsequent studies revealed that a lower catalyst loading (10 mol%) could be employed when a more electrophilic acyl pyrrole acceptor was used.[16]



Scheme 3 Synthesis of fused polycyclic ethers.

Xu and coworkers reported in 2012 a highly enantioselective intramolecular Stetter reaction on polyunsaturated substrates of type **43** (equation 9).[30] A variety of bases of varying strength were screened in conjunction with aminoindanol-derived triazolium salt **44** and the use of the relatively weak sodium acetate provided the best yields. High yields could be achieved even in the

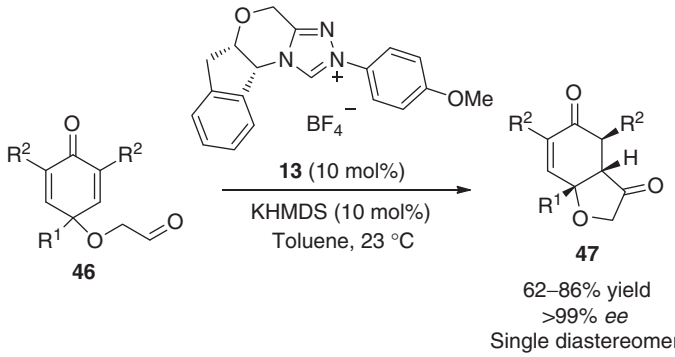
presence of only 2.5 mol% of the triazolium salt. Remarkably, it was found that the addition of catalytic amounts of acetic acid resulted in faster reactions and higher conversions to the desired cyclized product. The authors surmise that the acetic acid cocatalyst helps stabilize the active carbene, thus facilitating turnover of the catalyst.



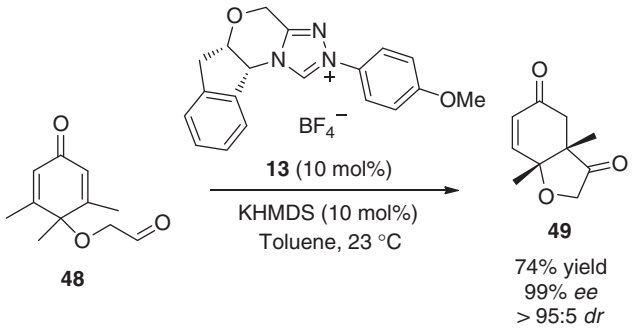
(9)

4.23.2.3 Desymmetrization Reactions

In 2006, Liu and Rovis introduced a new type of enantioselective intramolecular Stetter reactions that feature the desymmetrization of cyclohexadienones **46** to obtain hydrobenzofuranones **47** (equation 10).[31] The substrates for this transformation are easily prepared from the corresponding phenols via a hypervalent iodine-promoted oxidation in the presence of a glycol, followed by oxidation of the remaining primary alcohol to the required aldehyde. As was the case in other types of intramolecular Stetter reactions, the electronic nature of the *N*-aryl substituent on the triazolium catalyst had a profound impact on the outcome of the reaction. Aminoindanol-derived triazolium salt **13** bearing an electron-rich *p*-anisidyl substituent gave much higher enantioselectivities than its counterpart bearing an *N*-C_6F_5 substituent (88% *ee* versus 31% *ee* for $R^1 = CH_3$, $R^2 = H$). A variety of linear and branched alkyl groups are tolerated for both R^1 and R^2, and reactions were generally completed within 5 min. Other interesting features of these reactions include the possibility of forming carbocycles and quaternary stereocenters under the same conditions (equation 11), in addition to the demonstrated feasibility of a gram scale reaction at 3% catalytic loading.[32] It is also noteworthy that fragmentation of the substrate because of the presence of an α-reducible functionality does not compete with the desired process.[33–36]



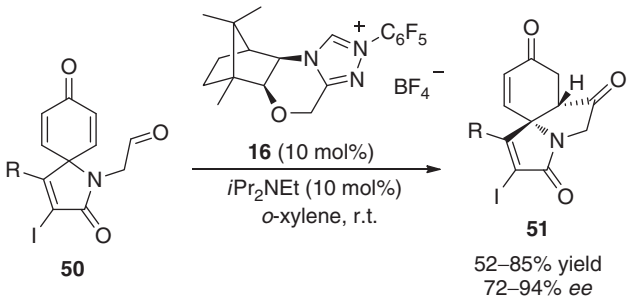
(10)



(11)

In a related work, Jia and You reported in 2012 the Stetter desymmetrization of bicyclic spirodienones **50** mediated by camphor-derived triazolium salt **16** (equation 12).[37] Interestingly, the camphor-derived catalyst bearing an *N*-C_6F_5 substituent

proved greatly superior in both yield and enantioselectivity to more electron-rich catalysts. In contrast, and in line with Liu and Rovis' results, the use of aminoindanol-derived catalyst **13** bearing the same *N*-C_6F_5 substituent led to a racemic mixture of the desired product. Although substitution on the lactam ring is tolerated, substituents on the cyclohexadienone moiety suppressed the reactivity under the reported conditions.



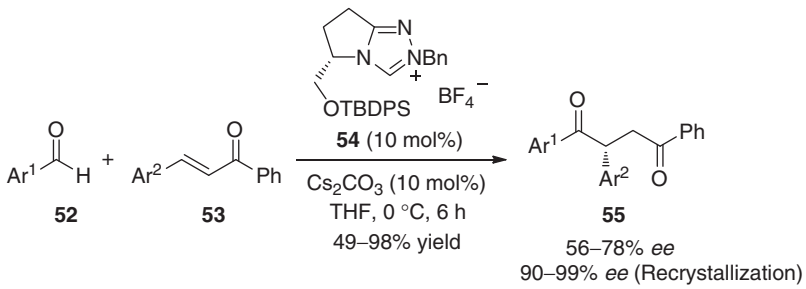
(12)

4.23.3 Intermolecular Stetter Reactions

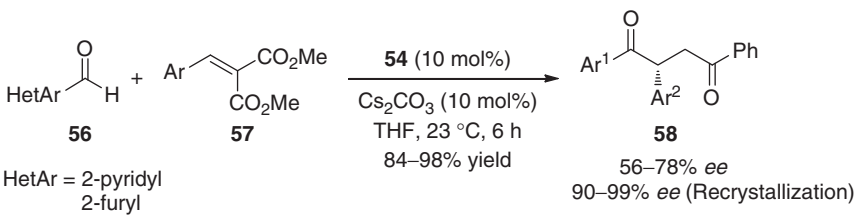
Following Stetter and coworkers' early work on the reaction that now bears his name, relatively few reports were published making use of this transformation in organic synthesis. Increased interest in the reaction arose via its intramolecular version as pioneered by Ciganek in 1995 (*vide supra*). Perhaps because of the additional difficulties associated with the development of an enantioselective version, the intermolecular variant of the Stetter reaction remained less explored for another decade.

4.23.3.1 Enantioselective Intermolecular Stetter Reaction

In recent years, significant progress has been made in the enantioselective intermolecular Stetter reaction. An early example reported by Enders and coworkers employed a chiral thiazolium catalyst in the Stetter reaction of butanal and *trans*-chalcone. The Stetter adduct was obtained in 39% *ee* and 4% yield (not shown).[38] In 2008, Enders and Balensiefer reported the first enantioselective intermolecular Stetter reaction achieving synthetically useful yields (and up to 78% *ee*), employing chiral triazolium catalyst **54** (equation 13).[39] Moderate to excellent yields and excellent enantiomeric excess values were obtained following recrystallization (up to >99% *ee*). The *N*-benzyl substituent on the catalyst plays a vital role in the reactivity, as the more commonly used *N*-aryl triazolium salts failed to catalyze the reaction. The scope of the reaction was at first limited to the combination of aromatic aldehydes (**52**) and chalcone derivatives (**53**) and later extended to the reaction of 2-heteroaromatic aldehydes (**56**) with arylidene malonates **57** (equation 14).[40]



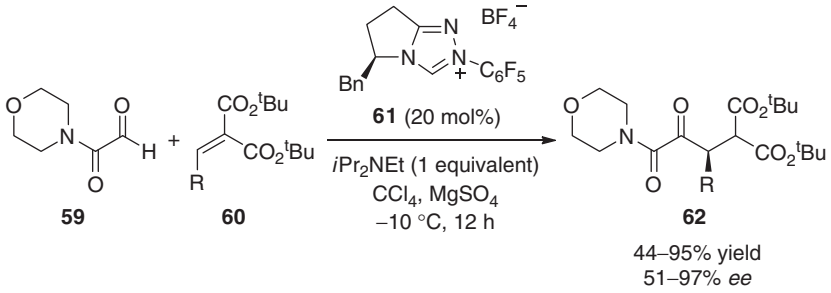
(13)



(14)

In 2008, Rovis and coworkers reported the first highly enantioselective intermolecular Stetter reaction. The use of triazolium precatalyst **61** afforded Stetter adducts **62** in moderate to excellent yield with moderate to excellent enantiomeric excess values (equation 15).[41] Although this methodology represented a significant advance, excellent enantioselectivities were only obtained

when glyoxamides (**59**) were reacted with di-*tert*-butyl alkylidene malonates (**60**). Following this report, Liu and Rovis demonstrated that the reaction could be extended to alkylidene ketoamides **64** (equation 16).[42] In this case, a diastereoselective protonation leads to adduct **65** containing two contiguous stereogenic centers. No epimerization was observed under the reaction conditions, as was expected because of the strong $A_{1,3}$ strain in the corresponding enolate. Unlike the products obtained when using alkylidene malonates **60** (cf. equation 15), the resulting adducts **65** can undergo chemoselective reactions at either carbonyl functionality of the *β*-keto amide moiety without creating a mixture of diastereomers.



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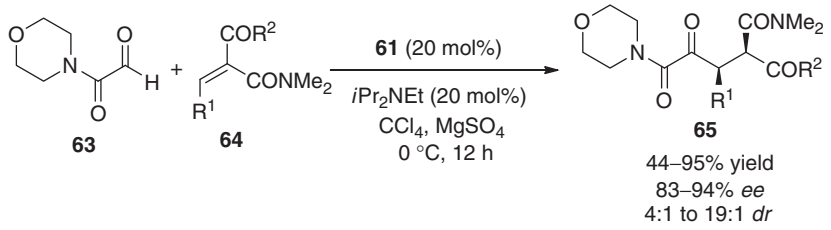
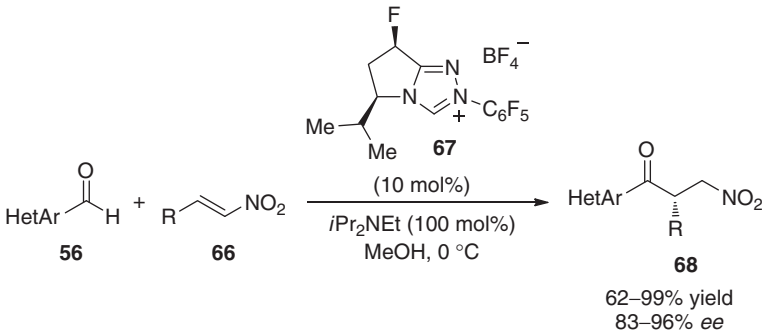


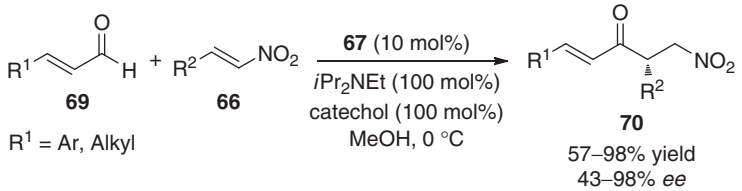
(16)

In 2009, Rovis and coworkers developed a new methodology making possible the use of singly activated acceptors for highly enantioselective intermolecular Stetter reactions.[43] The development of a new fluorinated triazolium salt proved critical to the success of the reaction between heteroaromatic aldehydes **56** and *β*-alkyl nitroalkenes **66** (equation 17). Superior yields and enantioselectivities were observed when *cis* fluorinated precatalyst **67** was employed compared to reactions in which the corresponding nonfluorinated or *trans* fluorinated salts were used. The efficiency of the catalyst was initially ascribed to conformational preferences dictated by stereoelectronic effects. However, subsequent computational studies suggested that an attractive electrostatic interaction between the C-F dipole and the developing negative charge on the nitronate is largely responsible for the spatial organization in the transition state when the *cis* fluorinated salt **67** is employed.[44]



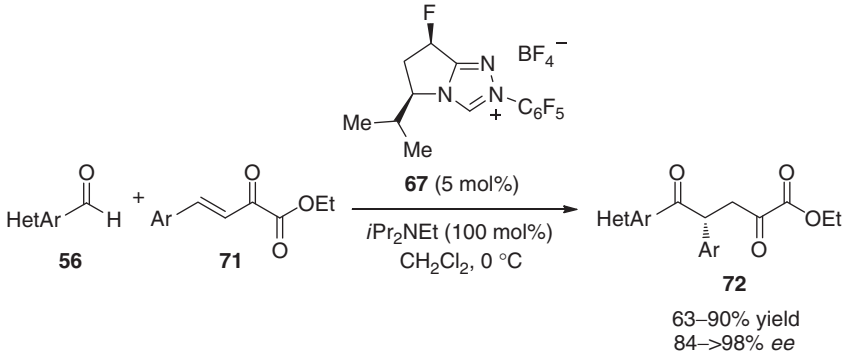
(17)

In 2011, DiRocco and Rovis extended the scope of the enantioselective Stetter reaction of *β*-alkyl nitroalkenes **66** to include enals (**69**) as the aldehyde moiety (equation 18).[45] Following a screen of various alcohol additives, the addition of catechol was observed to significantly improve the yield of the reaction. Furthermore, kinetic isotope effect studies suggest that the [1,2] proton shift to afford the Breslow intermediate is the turnover-limiting step. These combined results suggest that catechol, presumably in the form of catecholate, facilitates the proton transfer during that critical step.



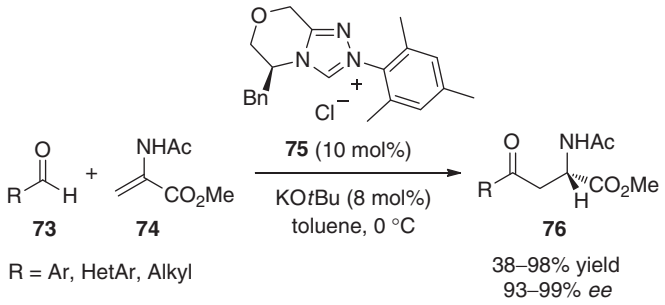
(18)

Subsequent to these studies, Gravel and coworkers reported the first highly enantioselective intermolecular Stetter reactions on substrates bearing aryl substituents on the reactive site of the acceptor (equation 19). The superior reactivity of β,γ-unsaturated α-ketoesters **71** compared to chalcone or nitroalkenes was demonstrated through competition experiments. A screen of chiral triazolium catalysts revealed that the *cis* fluorinated triazolium salt **67** developed by Rovis and coworkers is also well suited to reactions involving these acceptors. The reaction of β,γ-unsaturated α-ketoesters (**71**) with heteroaromatic aldehydes (**56**) generally afforded Stetter adducts **72** in excellent yields with good to excellent enantiomeric excess values (equation 19). Aromatic aldehydes afforded modest yields and moderate enantiomeric excess values.[46] The usefulness of the methodology was further demonstrated through chemoselective transformations of each carbonyl unit present in the Stetter adduct.



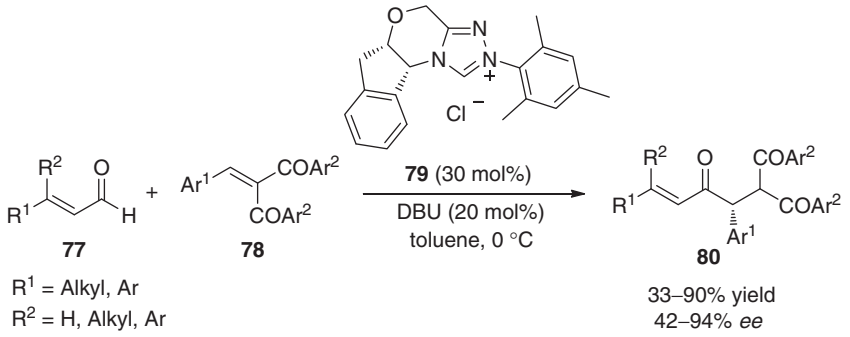
(19)

In 2011, Glorius and coworkers reported the enantioselective synthesis of amino acid derivatives **76** via the enantioselective intermolecular Stetter reaction of dehydroamino esters **74** (equation 20).[47] This methodology represents the first example of an enantioselective Stetter reaction of β-unsubstituted acrylate derivatives, demonstrating that high stereoselectivity can be obtained in the protonation step following attack of the Breslow intermediate. Although excellent enantiomeric excess values were consistently obtained for all aldehydes tested, the yield of the reaction ranged from modest to excellent. The reaction of dodecanal, the sole example using an aliphatic aldehyde, afforded a moderate yield (52%). Interestingly, the use of a strong base was found to be important to obtain a good yield and high enantiomeric excess.



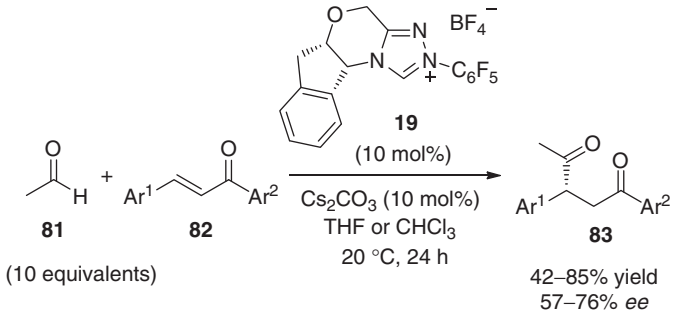
(20)

Also in 2011, Chi and coworkers reported the preparation of highly enantioenriched Stetter adducts from β-alkyl enals and 2-arylidene-1,3-diketones (equation 21).[48] Reactions employing β-aryl or β,β-disubstituted enals produced adducts in comparatively lower enantiomeric excess. Unsymmetrical arylidene diketones and arylidene ketoesters afforded products in excellent enantiomeric excess, albeit with little diastereoselectivity.



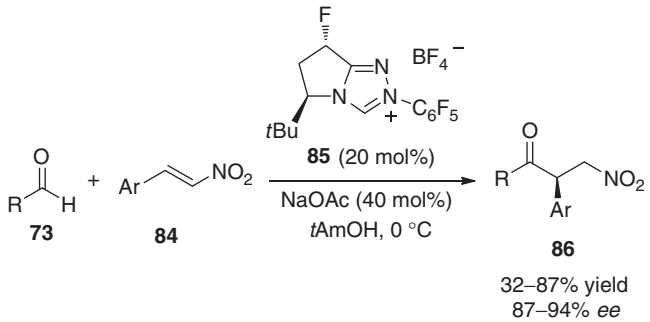
(21)

The first Stetter reactions involving acetaldehyde (**81**) were reported by Ryu, Yang, and coworkers in 2011 (equation 22).[49] Modest to good enantioselectivities were observed using *trans*-chalcone derivatives **82** and aminoindanol-derived triazolium salt **19**.



(22)

A 2012 report from Houk, Rovis, and coworkers disclosed the first highly enantioselective intermolecular Stetter reaction utilizing aliphatic aldehydes (equation 23).[50] When reacted with nitrostyrenes (**84**) in the presence of *trans* fluorinated triazolium salt **85**, unbranched aliphatic aldehydes generally afforded excellent yields. In contrast, the use of *β*-branched aldehydes afforded the products in poor yields whereas α-branched aldehydes were found to be unreactive under these conditions. Notably, Rovis and coworkers' previous work with *cis* fluorinated triazolium salt **67** and *β*-alkyl nitroalkenes afforded the product with opposite enantioselectivity (equation 17). A computational study on the reaction shown in equation 23 suggested the presence of an attractive electrostatic interaction between the backbone fluorine atom and the aromatic ring of the acceptor in the transition state, thus explaining the difference in the preferred catalyst between *β*-alkyl and *β*-aryl nitroalkene acceptors.



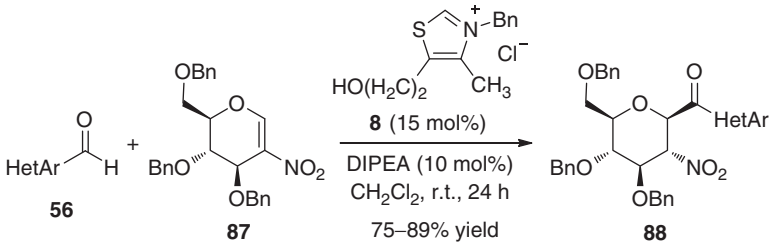
(23)

As seen in this section, a number of highly enantioselective intermolecular Stetter reactions have been reported over the past decade. However, the scope of the reaction still remains limited despite these achievements. For instance, no example of highly enantioselective couplings between aliphatic aldehydes and *β*-alkyl acceptors has been reported as of 2012.

In addition to these recent advances, the enantioselective synthesis of formal Stetter adducts has been achieved using aldehyde surrogates. A detailed discussion on the use of these surrogates is given in Section 4.23.6 (*vide infra*).

4.23.3.2 Diastereoselective Intermolecular Stetter Reaction

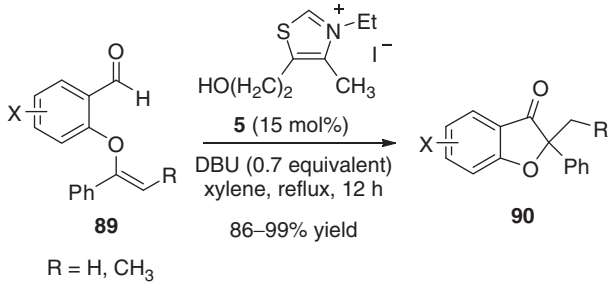
Few examples of diastereoselective intermolecular Stetter reactions have been reported in which either the aldehyde or the acceptor partner dictates the selectivity of the reaction by virtue of preexisting stereogenic centers. In 2011, Liu and coworkers reported the diastereoselective formation of *β*-*C*-glycosides **88** via the Stetter reaction of heteroaromatic aldehydes **56** (equation 24).[51] The observed selectivity is presumably the result of thermodynamic control, as the most stable 1,2-*trans* products were formed exclusively in all cases. Good yields were obtained when catalytic amounts of diisopropylethylamine were employed. Stoichiometric amounts of cesium carbonate afforded the elimination product ($-HNO_2$) when using either heteroaromatic, aromatic, or aliphatic aldehydes.



(24)

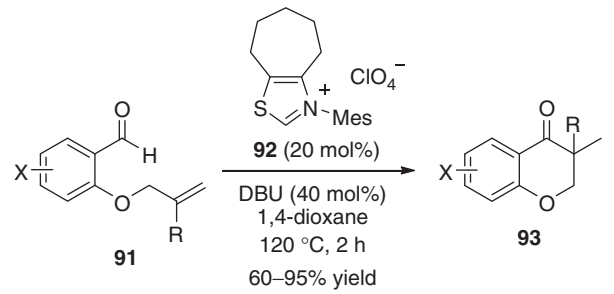
4.23.4 Hydroacylation Reactions

In 2008, She, Pan, and coworkers disclosed the hydroacylation of enol ethers (equation 25).[52] This new reaction is mechanistically similar to the thiazolium-catalyzed intramolecular Stetter reaction. However, the electrophilic Michael acceptor moiety is replaced by an enol ether. The reaction is tolerant to both electron-donating and electron-withdrawing substituents (X) on the aromatic tether. The authors propose a mechanism that features a concerted proton transfer during the enolamine attack onto the enol ether **89**. These results build on a related process in which enol ether intermediates were formed *in situ*.[53]



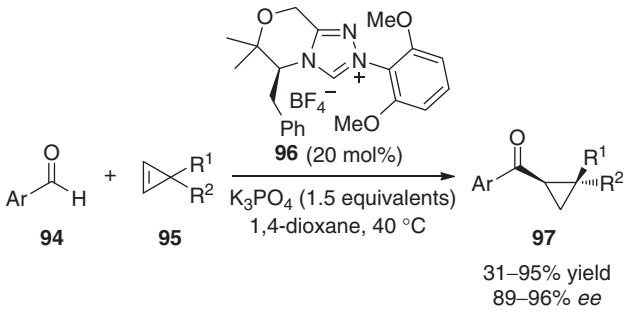
(25)

Glorius and coworkers subsequently found that unactivated alkenes (**91**, R=H) could also be used in intramolecular hydroacylations (equation 26).[54] The presence of a bulky *N*-Mes substituent on the thiazolium catalyst **92** proved to be crucial for this transformation.[55] Thiazolium catalysts bearing *N*-2,6-diisopropylphenyl or *N*-alkyl substituents perform poorly in these reactions, as do *N*-Ph and *N*-C_6F_5 triazolium and imidazolium salts. However, the successful use of chiral *N*-Mes triazolium salts allows the formation of quaternary centers (R=Ph) with high levels of enantioselectivity.[56] Calculations at the B2PLYP-D level support a concerted but asynchronous proton transfer in the enantioselectivity-determining step. Glorius and coworkers later extended the intramolecular hydroacylation reaction using *N*-Mes thiazolium salt **92** to tethered aromatic alkynes to obtain the corresponding enone products (not shown).[57]



(26)

The challenging intermolecular hydroacylation of alkenes and alkynes has been accomplished by Glorius and coworkers through the use of highly reactive substrates. Arynes formed *in situ* can be coupled to aromatic, heteroaromatic, aliphatic, as well as α,β-unsaturated aldehydes to provide aryl ketones.[58] Electron-poor aldehydes generally afforded the best yields. Cyclopropenes (**95**) were also found to be sufficiently reactive for intermolecular hydroacylations catalyzed by *N*-Mes triazolium salts.[59] The availability of chiral triazolium salts again led to the disclosure of an enantioselective version of this reaction (equation 27).[60] In this case, the use of an electron-rich *N*-2,6-$(MeO)_2C_6H_3$ substituent on triazolium salt **96** increased both the reactivity and selectivity over the reaction using the corresponding *N*-Mes substituted catalyst.



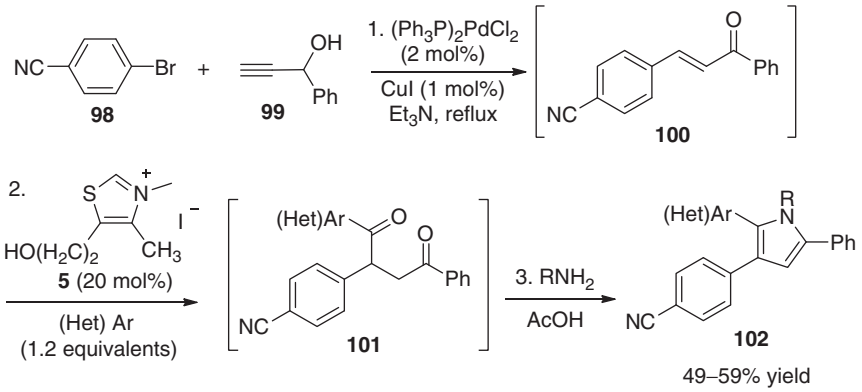
(27)

The equivalent transition metal-catalyzed hydroacylation of alkenes and alkynes has been known since the 1970s and has been reviewed elsewhere.[61]

4.23.5 Domino and One-Pot Reactions

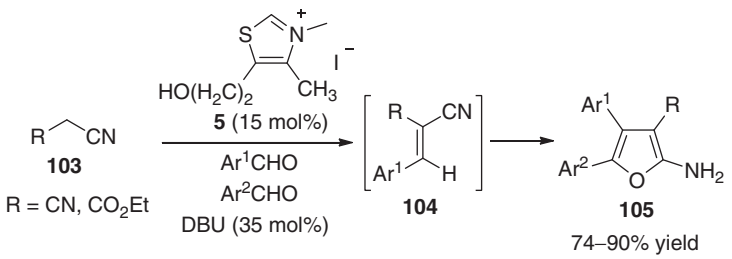
4.23.5.1 Synthesis of Heterocycles

The Stetter product's 1,4-difunctionalized relationship makes the adduct a common intermediate in the synthesis of heteroaromatic compounds such as pyrroles and furans. In 2001, Müller and coworkers reported the synthesis of 1,2,3,5-tetrasubstituted pyrroles **102** via a one-pot, four-component, coupling-isomerization-Stetter–Paal–Knorr pathway (Scheme 4).[62] In this process, the palladium-catalyzed coupling-isomerization reaction of propargyl alcohol **99** and aryl halide **98** produces the Stetter acceptor *in situ*. The subsequent NHC-catalyzed Stetter reaction affords a 1,4-diketone (**101**), which condenses with an amine in the Paal–Knorr reaction. A variety of amines were well tolerated in the Paal–Knorr condensation, allowing for variation in the pyrrole's *N* substituent. However, the electronic requirements of the Stetter reaction limit the 2, 3, and 5 positions of the pyrrole to aromatic and heteroaromatic substituents.



Scheme 4 One-pot coupling-isomerization-Stetter–Paal–Knorr for 1,2,3,5-tetrasubstituted pyrroles.

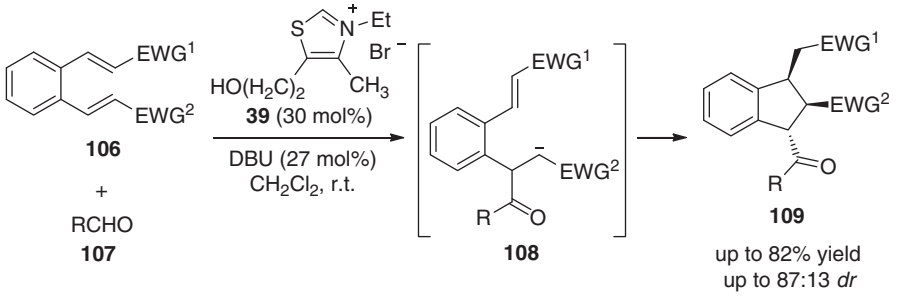
Hu et al. reported, in 2011, the synthesis of 4,5-diarylated-2-aminofuran-3-carbonitriles via a domino Stetter-γ-ketonitrile cyclization reaction.[63] Following the Stetter reaction of an arylidene malononitrile with an aromatic aldehyde, the product spontaneously cyclizes to afford a furan ring. Yao et al. also employed the Stetter reaction in the synthesis of fully substituted furans (Scheme 5).[64] Yao's one-pot, three-component methodology commences with the Knoevenagel condensation of malononitrile and one equivalent of aldehyde to afford the Stetter acceptor **104** *in situ*. A second equivalent of aldehyde undergoes a Stetter addition-cyclization sequence to afford furan **105**. When two aldehydes of different reactivity are employed, the reaction proceeds chemoselectively and the most electron-poor aldehyde forms the arylidene malononitrile, eventually affording the desired product in good yield. The protocol also allows the installation of 3-ethyl esters on the furan ring.



Scheme 5 One-pot Knoevenagel–Stetter-cyclization formation of 4,5-diaryl-2-aminofurans.

4.23.5.2 Synthesis of Carbocycles

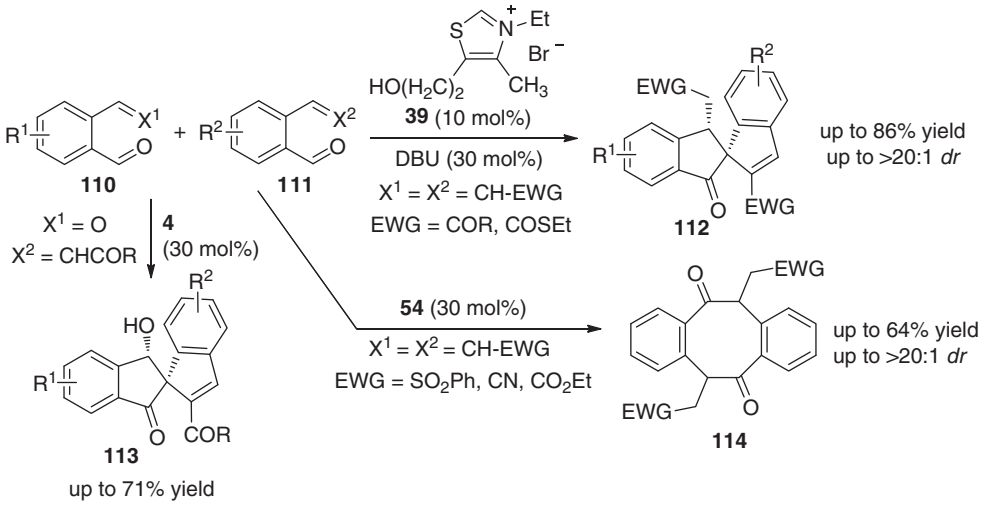
The ability to inexpensively produce complex structures from structurally simple starting materials has made domino reactions a popular tool in organic synthesis. The Stetter reaction's mild reaction conditions make it an excellent candidate for domino processes. Although the aforementioned multicomponent reactions involve *in situ* heterocyclization of the Stetter adduct, productive pathways can also be obtained from trapping the enolate intermediate formed during the Stetter reaction. The first demonstration of such an approach came in 2009, when Sánchez-Larios and Gravel reported a domino Stetter–Michael reaction of an aldehyde with a double Michael acceptor **106** (Scheme 6).[65] In this methodology, the anion **108** produced during the Stetter reaction is trapped in an intramolecular Michael reaction. The reaction produces indanes **109** bearing three contiguous stereogenic



Scheme 6 Domino Stetter–Michael reaction toward indanes.

centers. Good yields and diastereomeric ratios were obtained when electron-poor, unhindered aldehydes were employed. The more thermodynamically stable *all-trans* isomer could be obtained following a DBU-induced epimerization. When unsymmetrical acceptors were used (EWG^1 = CN, SO_2Ph, COMe; EWG^2 = COPh), the reaction proceeded chemoselectively, affording only one regioisomer. No enantioselective version of this domino reaction has been reported.

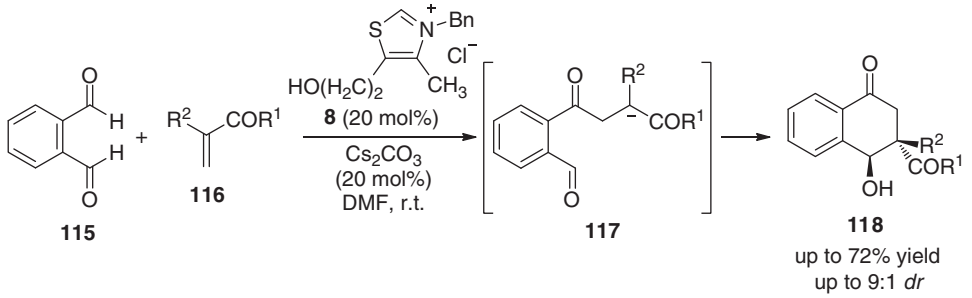
Gravel and coworkers pursued their work by reporting a domino Stetter-aldol–Michael dimerization of *o*-formyl chalcone derivatives (Scheme 7).[66] The rapid construction of three carbon–carbon bonds and a quaternary center produces spiro bis-indanes **112** in good to excellent diastereomeric ratios under mild reaction conditions. One example demonstrated that cross Stetter-aldol–Michael reactions are possible, provided that electronically biased starting materials are employed. Although thioesters were also well tolerated as electron-withdrawing groups, substrates bearing esters, nitriles, and sulfones were consumed in a double Stetter pathway to afford eight-membered diketones **114**.[67] This pathway was optimized through the use of the more reactive *N*-benzyl thiazolium salt **54** developed by Enders and coworkers (*vide supra*). The synthesis of spiro bis-indanes was also extended to the cross-dimerization of phthalaldehyde derivatives and *o*-formyl chalcones in a Stetter-aldol–aldol reaction. The Stetter-aldol–aldol products **113** were obtained in modest to good yield. However, poor diastereomeric ratios were obtained, presumably because of a rapid, base-promoted retro-aldol–aldol isomerization.



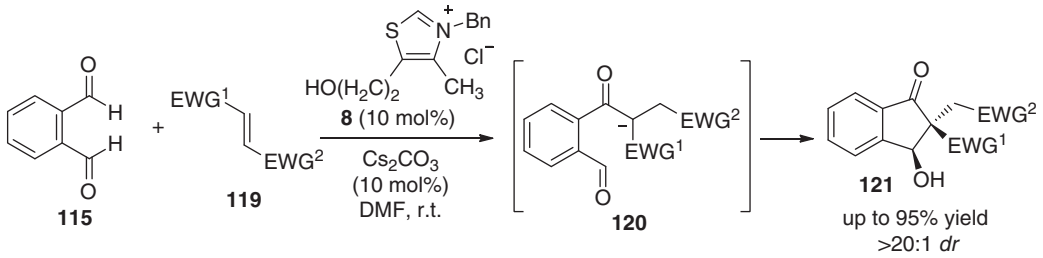
Scheme 7 Domino Stetter-aldol–Michael, Stetter–Stetter, and Stetter-aldol–aldol.

Early in 2010, Ye et al. reported the production of 4-hydroxytetralones via a domino Stetter-aldol reaction (Scheme 8).[68] Following the Stetter reaction of *o*-phthalaldehyde (**115**) and an electron-poor olefin (**116**), the anion **117** produced in the reaction undergoes an intramolecular aldol reaction with the free formyl group. Good yields and diastereomeric ratios of 4-hydroxytetralones **118** were obtained when mono-substituted olefins were employed. The use of α,α-disubstituted olefins as acceptors was also well tolerated. Interestingly, the domino Stetter-aldol reaction of the mono-substituted olefin favored the *trans* isomer whereas the *cis* isomer was favored in the corresponding stepwise process. As base-promoted *cis*/*trans* isomerization was proven to be insignificant, these results suggest that the NHC plays a role in inducing stereoselectivity in the aldol reaction.

The Ye group later extended the Stetter-aldol strategy with a [4 + 1] annulation that produces hydroxyindanones **121** from the Stetter-aldol reaction of *o*-phthalaldehyde **115** and 1,2-diactivated Michael acceptors **119** (Scheme 9).[69] The additional electron-withdrawing group facilitates a proton-transfer event, resulting in the formation of the kinetically favored five-membered ring. The reaction proceeds with excellent diastereoselectivity. Although other substrates were well tolerated, excellent yields were obtained



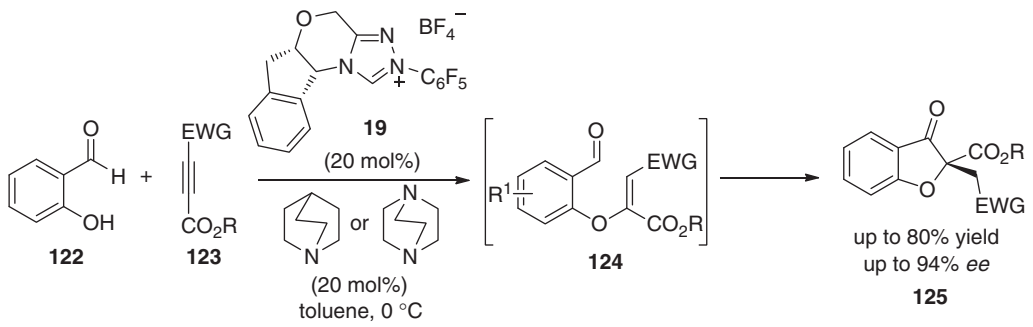
Scheme 8 [4 + 2] Stetter-aldol toward 4-hydroxytetralones.



Scheme 9 [4 + 1] Stetter-aldol toward hydroxyindanones.

when the Michael acceptor was doubly activated with an ester ($EWG^1 = CO_2Et$) and an electron-poor ketone (EWG^2 = COAr, COHetAr).

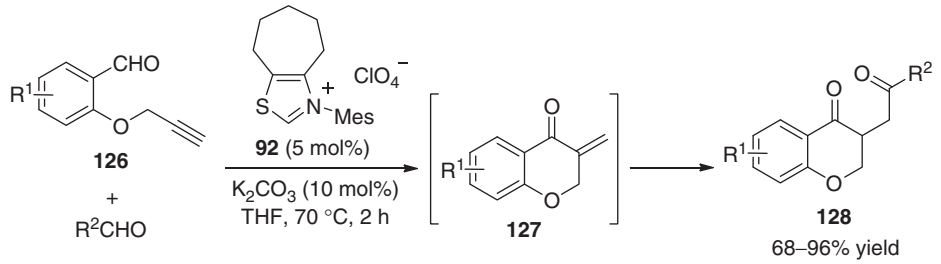
In 2010, Rovis and coworkers reported a cascade enantioselective oxa-Michael–Stetter reaction between salicylaldehydes **122** and activated alkynes **123** (Scheme 10).[70] An amine-catalyzed oxa-Michael reaction produces the Stetter acceptor **124** *in situ*. The subsequent intramolecular Stetter reaction is catalyzed by the carbene derived from chiral triazolium **19**. The product **125** bearing a quaternary center is formed in good to excellent enantiomeric excess. Notably, this one-pot procedure was reported to afford higher enantiomeric excess values than the corresponding two-pot process. Although symmetrical alkynes ($CO_2R = EWG = CO_2Me$) afforded excellent results, unsymmetrical alkynes (R = Me, Et; EWG = COAr, COAlkyl, $PO(OEt)_2$) afforded products in generally poor enantiomeric excesses and in poor to modest yield. An enantioselective oxa-Michael–Stetter reaction of salicylaldehyde derivatives and mono-activated terminal allenes in moderate yield and good to excellent enantiomeric excess was also disclosed in the same report (not shown).



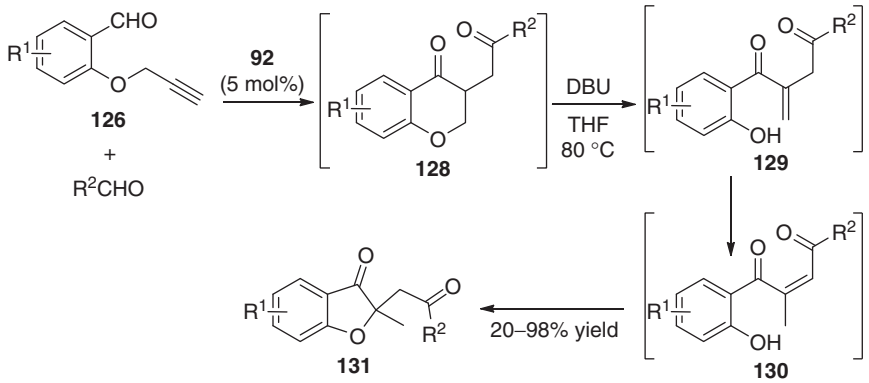
Scheme 10 Cascade enantioselective oxa-Michael–Stetter reaction.

In 2010, Glorius and coworkers reported a unique dually NHC-catalyzed cascade reaction (Scheme 11).[57] In this pathway, an intramolecular NHC-catalyzed hydroacylation of a terminal alkyne **126** produces the Stetter acceptor *in situ*. The resulting *β*-unsubstituted enone **127** then undergoes an intermolecular Stetter reaction to afford the chromanones **128** in good to excellent yield with a variety of aromatic, heteroaromatic, and aliphatic aldehydes.

Following this initial disclosure by Glorius et al., the groups of Glorius and Zeitler independently reported an extension of the hydroacylation-Stetter cascade reaction to the formation of benzofuranones (Scheme 12).[71,72] When strong bases are employed, the hydroacylation-Stetter product **128** undergoes a retro-Michael-isomerization sequence followed by an intramolecular oxa-Michael reaction to afford disubstituted benzofuranones **131**, generally in good to excellent yields.



Scheme 11 Chromanone synthesis via a cascade hydroacylation-Stetter reaction.



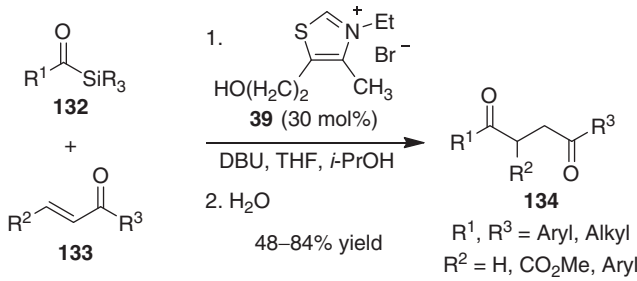
Scheme 12 Cascade synthesis of benzofuranones.

4.23.6 Other Sources of Acyl Anion Equivalents

The use of acyl anion equivalents from sources other than aldehydes provides certain advantages in expanding the scope of the Stetter reaction. Primarily, the kinetically favored self-condensation of the aldehyde (benzoin reaction) is circumvented by the absence of aldehyde in the reaction mixture. Furthermore, and unlike the NHC-catalyzed reaction of aldehydes, some acyl anion equivalent sources do not require basic conditions, thus allowing for Stetter-like additions to be performed on base-sensitive starting material.

4.23.6.1 Acyl Silanes

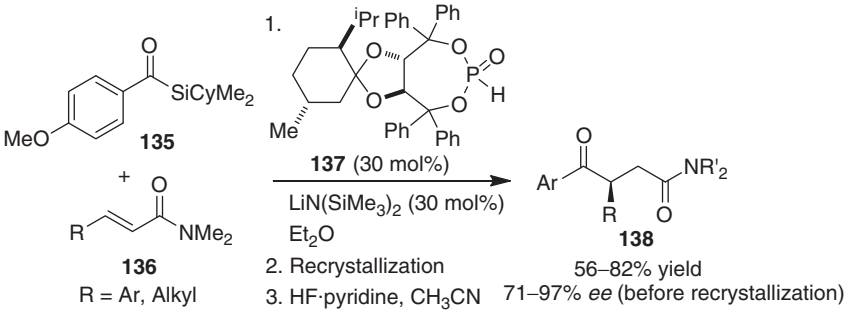
Scheidt and coworkers reported the first NHC-promoted formal Stetter reaction of acyl silanes in 2004 (equation 28).[73] The proposed reaction mechanism commences with the addition of the NHC derived from thiazolium salt **39** onto the carbonyl of the acylsilane **132**. Subsequently, a [1,2]-Brook rearrangement affords the silylated Breslow intermediate. Isopropanol-promoted desilylation produces the Breslow intermediate, which then reacts with the Michael acceptor to form a formal Stetter adduct **134**. The scope of the reaction is limited to unsubstituted β-aryl and β-alkoxycarbonyl Michael acceptors **133**. However, both aromatic and aliphatic acyl silanes were well tolerated. This methodology was subsequently used in one-pot furan and pyrrole syntheses.[74,75]



(28)

Subsequent to the disclosure on the formation of racemic sila-Stetter adducts, Johnson and coworkers reported the enantioselective formal Stetter reaction of acyl silanes (equation 29).[76,77] Previously, Johnson had employed this methodology in

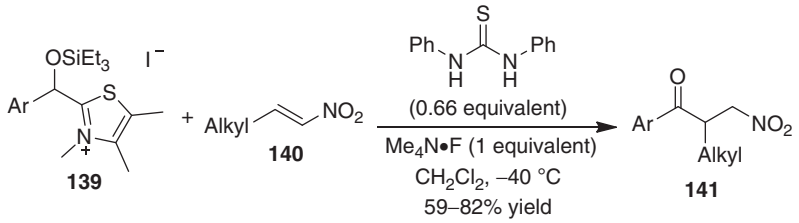
cyanide-promoted and chiral metallophosphite-promoted sila-cross-benzoin reactions.[78,79] The metallophosphite derived *in situ* from **137** and LiHMDS was employed to activate the acyl silane **135** and direct the stereoselectivity of the sila-Stetter reaction. Addition of the silylated Breslow intermediate onto the acceptor **136**, followed by silyl group transfer, affords the enantioenriched silylated Stetter product. Recrystallization of the adduct followed by desilylation affords the formal Stetter product **138** in enantiomeric excesses superior to the values obtained for any intermolecular Stetter reaction reported at the time (up to 99% *ee*). This methodology also highlights the use of poorly reactive unsaturated amides in formal Stetter reactions.



(29)

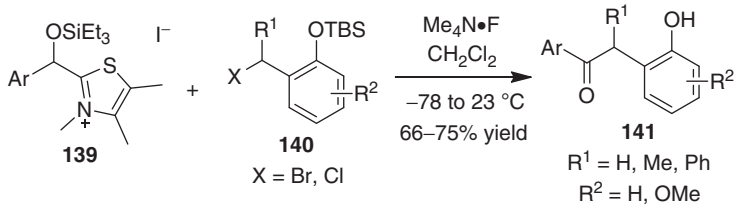
4.23.6.2 Silylated Thiazolium Carbinols

To test the feasibility of the proposed mechanistic pathway for their acyl silane reaction shown in equation 28, Scheidt and coworkers prepared the intermediate silylated thiazolium carbinol and subjected it to the reaction conditions (DBU, THF, and *i*-PrOH). Under these conditions, the silylated thiazolium carbinol afforded the formal Stetter product in 60% yield.[75] Following this discovery, the viability of silylated thiazolium carbinols as acyl anion equivalents in Stetter-like additions was further investigated. In this reaction, a fluoride source desilylates the thiazolium carbinol **139** and a proton transfer affords the corresponding Breslow intermediate that subsequently participates in the conjugate addition (equation 30).[80] This unique process for Breslow intermediate generation does not require the use of a base and therefore allows formal Stetter reactions to be performed on base-sensitive *β*-alkyl nitroolefins **140**. Superior results were obtained when a thiourea additive was employed to activate the nitroalkene via hydrogen bonding. Interestingly, the use of a chiral quinine-derived thiourea additive afforded the formal Stetter product **141** with good enantioselectivity (74% *ee*).



(30)

Mattson and Scheidt later combined this methodology with the fluoride-promoted *in situ* generation of *o*-quinone methides from *O*-silylated phenols toward the synthesis of *α*-aryl ketones **141** (equation 31).[81] Although various substituents on phenol **140** were well tolerated, aryl thiazolium carbinols **139** afforded products in better yields than alkyl or alkenyl thiazolium carbinols.

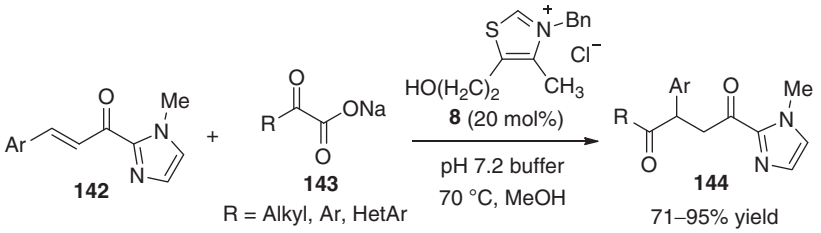


(31)

4.23.6.3 α-Keto Carboxylates

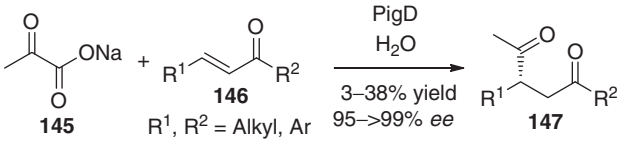
In 2005, Scheidt and coworkers reported the use of *α*-keto carboxylates **143** as acyl anion equivalents in Stetter-like additions (equation 32).[82] Initially, the authors sought to employ *α*-keto carboxylic acids as carbonyl anion equivalents in a biomimetic fashion. However, initial studies indicated that sodium carboxylates afforded results superior to those obtained from the corresponding carboxylic acids. Mechanistically, attack of the thiazolium-derived NHC onto the keto moiety followed by

decarboxylation affords the Breslow intermediate that ultimately forms the formal Stetter adduct **144.** Although a number of diverse α-keto carboxylates were well tolerated, the scope of the reaction was limited to α,β-unsaturated imidazole ketones **142** bearing β-aryl groups.



(32)

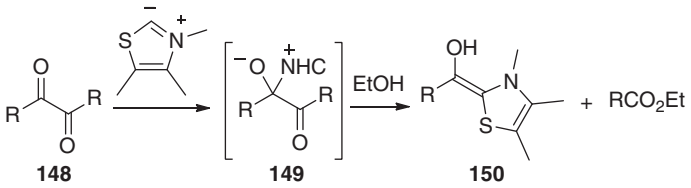
Following the work of Scheidt et al., Müller and coworkers reported the enantioselective formal Stetter reaction of pyruvate **145**, employing the thiamine diphosphate-dependent enzyme PigD as catalyst (equation 33).[83] Although the reported conditions provided access to formal Stetter products **147** of acetaldehyde in excellent enantiomeric excess, the products were generally isolated in modest yields. Interestingly, the low yields were in part attributed to the competing formation of 1,2 addition products from the enone **146** (formal benzoin reaction).



(33)

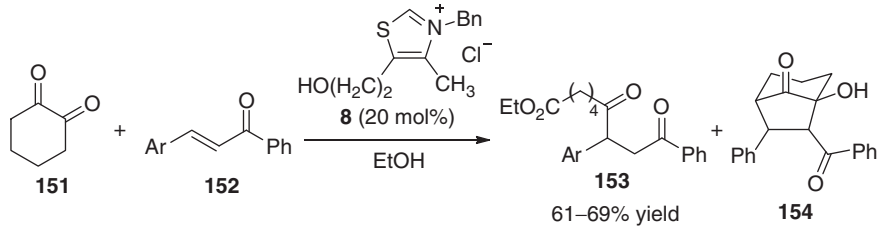
4.23.6.4 α-Diketones

In 2011, Massi and coworkers reported the formal Stetter reaction of alkyl α-diketones.[84] In the proposed mechanism, attack of the NHC on the diketone **148** affords a tetrahedral alkoxide **149** (**Scheme 13**). Acyl transfer of the remaining carbonyl group onto ethanol simultaneously affords the corresponding ethyl ester and the Breslow intermediate **150**. A variety of Stetter acceptors were well tolerated when 2,3-butadione and 3,4-hexadione were employed as substrates.



Scheme 13 Formation of Breslow intermediates from α-diketones.

The methodology developed by Massi and coworkers was extended to cyclic α-diketones (equation 34). By tethering the two carbonyl groups, the generation of the Breslow intermediate is simultaneously coupled with the production of a useful ester moiety on the same chain. Reaction of cyclic α-diketones **151** with chalcone derivatives **152** afforded products **153** in good yield, despite the competing formation of a domino Michael-aldol reaction product (**154**). Notably, when the unsymmetrical diketone 5-methyl-1,2-cyclopentadione was employed, the reaction proceeded regioselectively, affording the desired product in 48% yield (not shown).

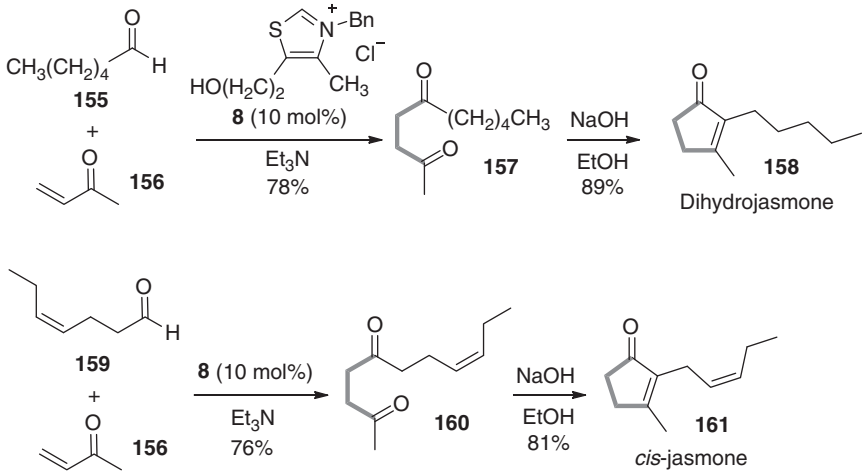


(34)

4.23.7 Natural Product Synthesis

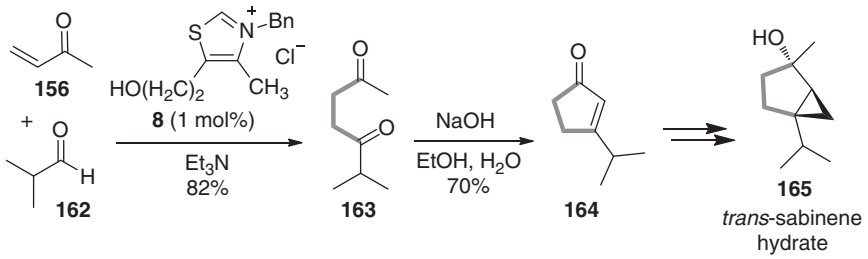
4.23.7.1 Syntheses Utilizing an Intermolecular Stetter Reaction

The 1,4-dicarbonyl relationship present in Stetter adducts has been exploited in a number of total syntheses. In 1975, Stetter and Kuhlmann reported the first application of the intermolecular Stetter reaction in natural product synthesis. Both dihydrojasmone and *cis*-jasmone were prepared by an intermolecular Stetter reaction and subsequent intramolecular aldol condensation of the Stetter adducts (Scheme 14).[85]



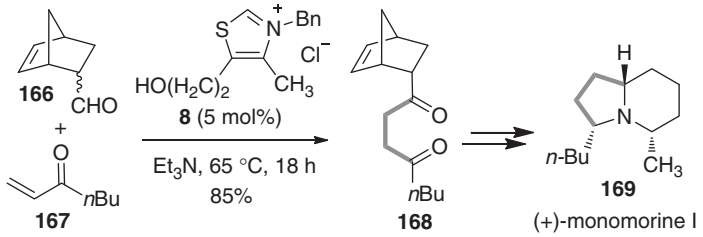
Scheme 14 Synthesis of dihydrojasmone and *cis*-jasmone.

In 2001, Galopin employed a similar Stetter-aldol methodology to form the five-membered ring in the synthesis of (±)-*trans*-sabinene hydrate **165** (Scheme 15).[86] Subjection of the aldol adduct **164** to the Corey–Chaykovsky reagent, followed by reduction of the epoxide, afforded racemic *trans*-sabinene hydrate.



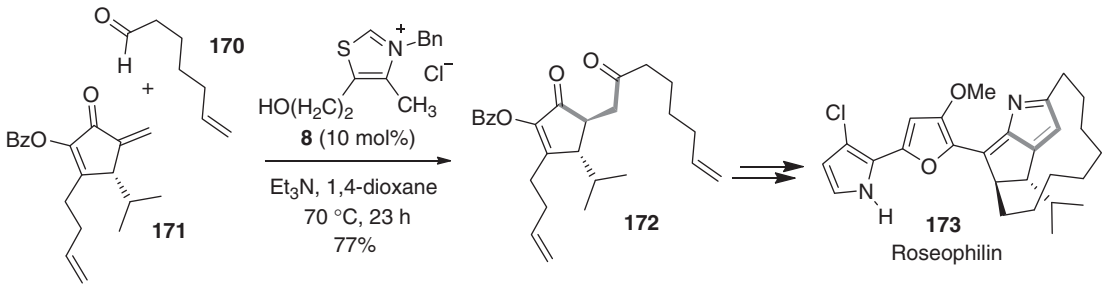
Scheme 15 Synthesis of *trans*-sabinene hydrate.

Randl and Blechert also took advantage of the Stetter adduct's 1,4-dicarbonyl relationship to form the pyrrolidine moiety in (+)-monomorine I (**169**) (Scheme 16).[87]



Scheme 16 Synthesis of (+)-monomorine I.

In the synthesis of the natural product roseophilin, Harrington and Tius employed a chiral auxiliary-controlled Nazarov cyclization to prepare α-methylene cycloketone **171** (Scheme 17).[88] The subsequent diastereoselective intermolecular Stetter reaction proceeded smoothly to provide the key intermediate **172** en route to roseophilin (**173**).

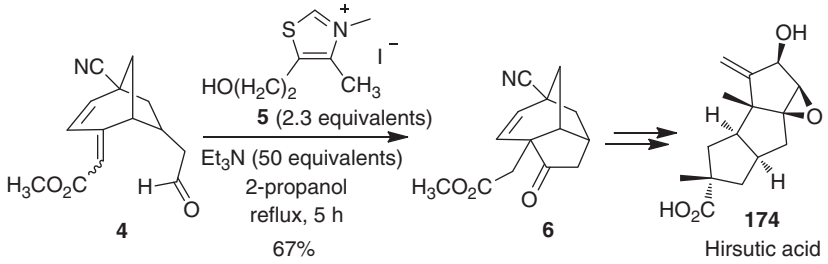


Scheme 17 Synthesis of roseophilin.

As can be seen in Section 4.23.7.1, all examples of intermolecular Stetter reactions utilized in natural product synthesis have so far been limited to the use of β-unsubstituted acceptors. Recent progress in intermolecular Stetter reactions, including enantioselective variants, promises to increase the appeal of the Stetter reaction in synthetic strategies.

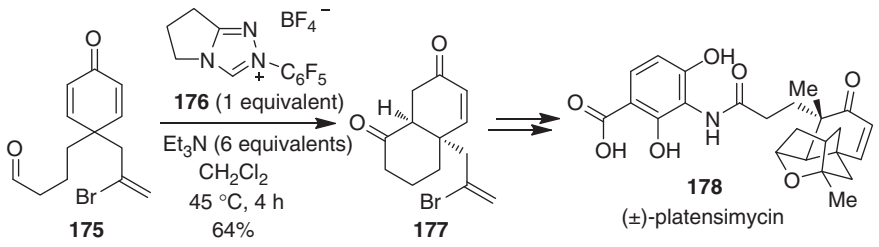
4.23.7.2 Syntheses Utilizing an Intramolecular Stetter Reaction

The intramolecular version of the Stetter reaction has also been employed in natural product synthesis. In 1979, Trost et al. employed an intramolecular Stetter reaction in the synthesis of hirsutic acid **174** (Scheme 18).[8] The challenging cyclization of substrate **4** proved quite efficient when an excess of inexpensive thiazolium salt **5** was used.



Scheme 18 Synthesis of hirsutic acid.

In 2007, Nicolaou et al. reported the formal synthesis of the antibiotic (±)-platensimycin (**178**) employing a diastereoselective intramolecular Stetter reaction to afford the racemic *cis*-decalin intermediate **177** (Scheme 19).[89] This reaction is conceptually similar to the desymmetrization reaction reported by Liu and Rovis a year earlier (equation 10), except that a new six-membered ketone is formed in this case. No mention is made of the performance of chiral triazolium salts in this reaction, perhaps highlighting a current limitation of the methodology.

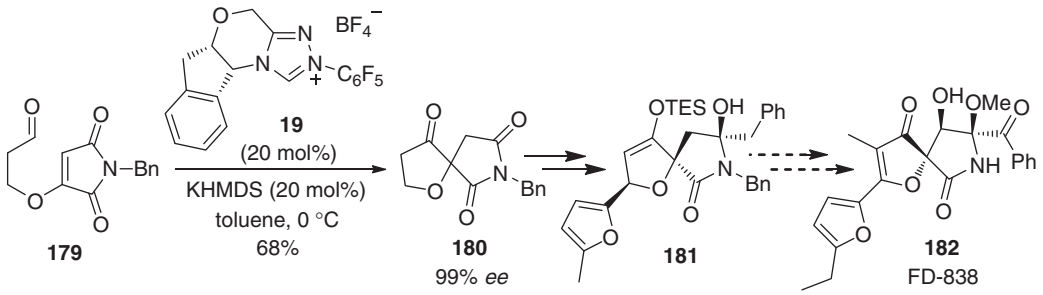


Scheme 19 Synthesis of (±)-platensimycin.

Orellana and Rovis reported the only example so far of an enantioselective Stetter reaction toward a natural product synthesis (Scheme 20).[90] The key step afforded the spirocyclic compound **180** with very high enantioselectivity, although determination of the absolute configuration proved elusive. Further elaboration toward the target was realized, but a completed synthesis of the densely functionalized antibiotic FD-838 (**182**) has not been reported.

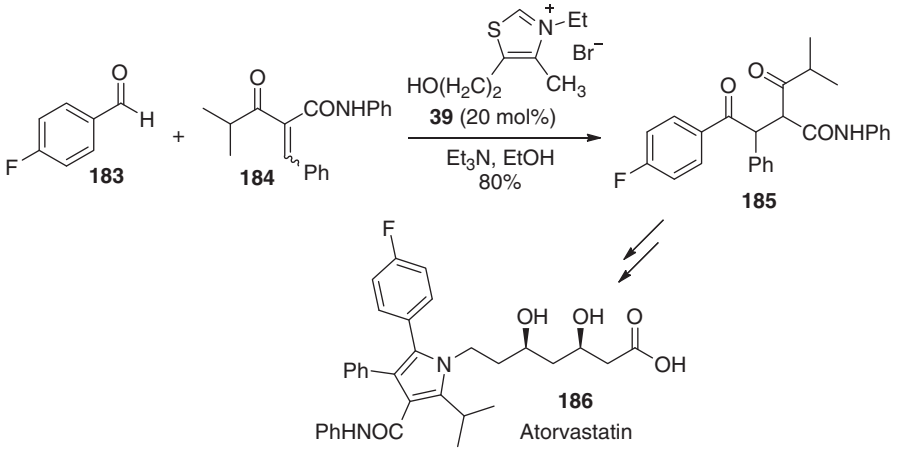
4.23.7.3 Syntheses of Nonnatural Products

In addition to natural products, the Stetter reaction has been used in the synthesis of medicinally relevant nonnatural products. The HMG-CoA reductase inhibitor atorvastatin (**186**), sold under the trade name Lipitor®, was synthesized in a convergent



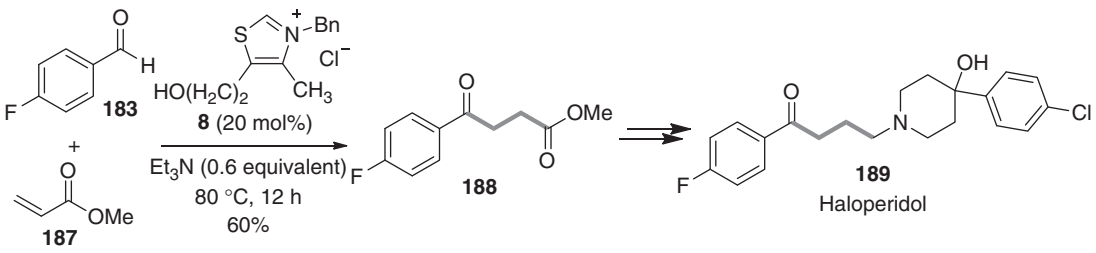
Scheme 20 Synthesis of the spirocyclic core of FD-838.

manner via a late-stage formation of its pyrrole core (Scheme 21).[91,92] This pyrrole formation relies on the well-known Paal–Knorr cyclocondensation of 1,4-diketones and primary amines. The required 1,4-diketone intermediate **185** is obtained from the Stetter reaction between *p*-fluorobenzaldehyde (**183**) and doubly activated acceptor **184**. The inexpensive thiazolium salt **39** is used for this pivotal transformation that was used in the industrial route.



Scheme 21 Synthesis of atorvastatin.

In their concise synthesis of the antipsychotic haloperidol, Grée and coworkers employed a Stetter reaction to generate the required 1,4-dicarbonyl intermediate **188** (Scheme 22).[93] This structural motif was then elaborated further to the γ-aminoketone motif found in haloperidol (**189**).



Scheme 22 Synthesis of haloperidol.

4.23.8 Summary

Although discovered in the 1970s, the Stetter reaction only became the focus of increased attention by various groups in the closing years of the twentieth century. Particularly significant have been efforts aimed at providing enantiomerically enriched Stetter products, first in the intramolecular variant and recently in the intermolecular version. Several addition types remain challenging despite these advances, particularly those involving alkyl-substituted acceptors and hindered substrates. Although

thiazolium and triazolium salts have been the catalysts of choice for the Stetter reaction, concurrent progress using NHC ligands in transition metal catalysis points to possible new heterocyclic motifs for the development of methodologies featuring wider or complementary scope. Application of the Stetter reaction to natural product synthesis has not been widespread, but recent advances make this reaction an increasingly appealing option in synthetic endeavors.

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